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White Blood Cell Growth Factor Utilization among Metastatic Colorectal Cancer Patients: Findings from a Multi-Center Oncology Practice Network

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White Blood Cell Growth Factor Utilization among Metastatic Colorectal Cancer Patients: Findings from a Multi-Center Oncology Practice Network

by

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Dedication

To the Almighty God who granted me the grace and fortitude to take on this chapter of my life. And to my parents Sir Innocent & Lady Veronica Orji, with love, for their immeasurable care and support.

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The Igbo say ora na azu nwa, and how accurate that is. Since man is not a solitary being, I'd say the success of this project was largely due to the help and efforts of my strong support system. I am deeply grateful to my academic supervisor, Dr. Carolyn Brown for her mentorship from the conception to completion of this thesis. Thank you for allowing me to take on this formidable project, for teaching me courage and patience even in moments of uncertainty, and for all I have learned from you. I want to thank my committee members whose inputs and feedback were critical in shaping this research work. Big thanks to Dr. Russell Hoverman for his substantial investments of time, efforts and expertise into this project, despite his busy schedule. It was a huge opportunity to work with and learn from you. I am extremely grateful to Dr. Kristin Richards for all her advice and assistance, especially in the course of obtaining and analyzing the data, and for painstakingly editing this work.

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Abstract

White Blood Cell Growth Factor Utilization among Metastatic Colorectal Cancer Patients

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Despite the widespread success of chemotherapy in treating various forms of cancer, its use is limited by certain toxicities like neutropenia. Colony stimulating factors (CSF), when used prophylactically, are useful in preventing febrile neutropenia (FN), as well as reducing its duration and severity. The American Society of Clinical Oncology (ASCO) guidelines recommend CSF for prophylaxis in cancer patients, but also recommend chemotherapy dose reduction as a viable alternative. The goal of this research was to assess and compare the use of CSF and dose reduction among metastatic colorectal cancer patients and factors that influence their use. The study also tested the impact of a program initiative on CSF prescription patterns.

For this retrospective observational study, data were obtained from the electronic health records of metastatic colorectal cancer patients who received care at a multi-center oncology practice network in two time periods. The outcomes of interest were CSF use,

chemotherapy dose reduction and all-cause mortality. Logistic regression techniques were utilized in exploring the relationships between these outcomes and some variables namely age, gender, FN risk, line of therapy, duration of treatment, year of diagnosis and disease . In 2016, a site-wide program initiative was introduced in the oncology practice network, with an aim of improving appropriate use of CSFs and compliance to guidelines on CSF use. The study had a total of 3426 regimens, corresponding to 2968 unique patients. A total of 11% of the patients used CSF (N=387). CSF use was significantly lower in the post-period, compared to the pre-period ($p<0.0001$). Compliance to guidelines was significantly higher in the post-period, compared to the pre-period ($p<0.0001$). Among subjects who had data on dose reduction (N=508), 58.7% received dose reduction distinctively. Factors that were significantly associated with CSF include age, FN risk, gender, line of therapy and duration of treatment. Factors associated with dose reduction include FN risk and duration of treatment, while factors associated with mortality include age, line of therapy, duration of treatment and gender. The study found no difference in mortality between CSF users and patients who received dose reduction ($p=0.2030$).

Program initiatives have the potential to positively impact prescription patterns. Also, there was no benefit of CSF use over dose reduction in terms of mortality. These conclusions could help decrease CSF overutilization and result in enhanced clinical practice and cost savings, without compromising health outcomes.

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CHAPTER 1: INTRODUCTION

This chapter introduces colorectal cancer, colorectal cancer treatment options and treatment complications. It also presents colony-stimulating factors (CSFs) and their clinical uses. Finally, it explains the objectives of the study and its significance.

1.1 COLORECTAL CANCER

Among cancers that affect both males and females, colorectal cancer is the third most common cancer and the second leading cause of cancer mortality in the United States. The American Cancer Society (ACS) projects that in 2018 there will be 97,220 cases of colon cancer and 43,030 cases of rectal cancer with 50,630 combined deaths.[1] Colorectal cancer was the leading cancer killer in the United States in the late 1940s and early 1950s.[2] However, incidence and mortality rates have declined overtime. This decline is attributed to early detection due to increased screening adherence and varying patterns of risk factors.[3] While overall death rates have been decreasing, incidence has been on the increase amongst young adults. For patients 20 to 34 years of age, incidence rates of both colon and rectal cancers have been on the rise. Researchers estimate that in 2030, incidence rates for colon cancer will grow by 90 percent for people aged 20 to 34 and by 28 percent for patients 35 to 49 years, whereas there will be a 38 percent decrease for people aged 50 to 74 years and a 45 percent decrease for individuals aged 75 and older.[4]

Efforts to reduce colorectal cancer incidence have focused on early detection via screening. Screening can prevent colorectal cancer by detecting growths at an early and treatable stage.[3] Generally, it is recommended by medical groups that individuals whose

risk is average begin screening at age 50. The United States Preventive Services Task Force (USPSTF) strongly propose screening to continue up to age 75; after that, screening should be based on individual patient characteristics. Screening for people older than 85 years is not recommended.[5] Both USPSTF and ACS have several suggested screening test options that differ in reliability, potential harm and costs.

Colorectal cancer imposes a considerable economic burden on society. A 2000 study estimated the economic burden of colorectal cancer in the United States to be in the range of $5.5 to 6.5 billion a year.[6]

1.2 Colorectal Cancer Treatment

The treatment of colorectal cancer largely depends on the spread of disease, but in general, the 3 standard treatments include surgery, chemotherapy and radiation therapy. Surgery involves an operation in which the cancer is removed. Chemotherapy involves the use of drugs to alter growth of cancer cells, either by cell destruction or hindering cell division. When chemotherapy is given by oral administration or via injection into the body, it is called systemic chemotherapy. When chemotherapy is administered in a specific body region or target site, it is known as regional chemotherapy. In radiation therapy, X-rays are used to kill the cancer cells, to shrink tumors prior to surgery or for symptom relief. External radiation therapy beams radiation to the tumor from the exterior, while internal radiation therapy means placing a radioactive substance close to or directly on the tumor.[7]

1.3 TREATMENT COMPLICATIONS

Despite the widespread use and success of chemotherapy in treating various forms of cancer,[8] it's use is limited by certain toxicities.[9] Colorectal cancer patients, and all cancer patients who undergo chemotherapy, are likely to have complications such as neutropenia.[10] Neutropenia is the leading toxicity of chemotherapy.[10] It has been shown to be life threatening, and occurs in 10 to 50 percent of treated patients.[11] Febrile neutropenia (neutropenia with fever) (FN) has been associated with significant morbidity and mortality and can lead to dose reductions and delays which could severely impact the effectiveness of chemotherapy.[12]

Neutropenia is characterized by a substantial reduction in neutrophils. Neutrophils are the most common and important type of white blood cells. They serve as the body's first major defense against infections because they are vital for fighting bacteria. In adult patients, neutropenia is defined as 1500 or less neutrophils per microliter of blood, while a count of below 500 per microliter of blood is considered severe.[13] Although neutropenia is often triggered by chemotherapy, other possible causes include Shwachman-Diamond syndrome, Fanconi anemia, severe aplastic anemia, leukemia, viral illnesses and bone marrow conditions. Some conditions that increase the risk of neutropenia include cancer, leukemia, a weak immune system, chemotherapy and radiotherapy.[14]

While neutropenia does not usually present with symptoms, it leads to an increase in risk of infection in the body.[13] Several tests may be used to assess neutropenia in patients. Some of the tests include a complete blood count (CBC) that measures neutrophil counts, an antibody blood test that checks for autoimmune neutropenia, bone marrow cell tests,

bone marrow trephine biopsy and cytogenetic and molecular testing of cell structures.[14] Mostly, neutropenia is treated using CSFs (colony stimulating factors), including G-CSF and GM-CSF. G-CSFs are a synthetic copy of the hormone that leads to growth of neutrophils in the bone marrow. Therefore, G-CFSs can increase neutrophil count. GM-CSF is a naturally produced glycoprotein with a similar function as G-CSF. Prophylactic antibiotics may also be administered.[13] Sometimes bone marrow transplants can be included in treatment when the G-CSFs are not effective or when leukemia is present.[14]

1.4 COLONY-STIMULATING FACTORS

Colony-stimulating factors , also called white blood cell growth factors, are medications that stimulate white blood cell production in the body. Clinically, they are used for chemotherapy induced marrow damage and neutropenia. CSFs, when used for prophylaxis, are useful in preventing neutropenia in response to chemotherapy, by reducing its duration and severity.[15] CSFs are supportive medications because they do not treat cancers; rather they prevent the occurrence of the side effects of cancer treatment, such as infections. Pegylated GCSFs are usually administered once per cycle, as injections 24 hours after chemotherapy. One of the benefits of CSF medication is that it lowers the likelihood of hospitalization for febrile neutropenia. However, CSF administration involves multiple injections to deliver the medication which could lead to fever and bone pain.[16] The four distinct types of CSFs include GM-CSF, G-CSF, MCSF and multipotential CSF (interleukin3).[17]

Currently, the American Society of Clinical Oncology (ASCO) recommends primary prophylactic use of CSF in cancer patients when the risk of febrile neutropenia is equal to or greater than 20 percent and secondary prophylaxis for patients who have experienced a complication from previous CSF use. CSF use is not recommended in patients who have a low or intermediate risk of febrile neutropenia. However, equally effective and safe chemotherapy regimens that do not require CSF support, as well as dose reduction or delay are also recommended as reasonable alternatives to CSF administration.[18]

1.5 THE RESEARCH PROBLEM

While CSFs have been shown to be useful in neutropenia prevention and management among cancer patients, studies suggest that they are being used outside of clinical practice recommendations.[19] This misuse is characterized by both underutilization and overutilization and has been linked to several patient and physician factors.[20] Some studies have researched on factors associated with CSF use in various populations of cancer patients. A population-based observational study in a cohort of lung and colorectal cancer patients found risk regimen and comorbidity to be among the associated factors.[21] Another study indicated that chemotherapy cycle and risk associated with chemotherapy regimen are predictors of CSF administration in elderly cancer patients.[22]

The aim of this study was to describe the characteristics of CSF users in a cohort of metastatic colorectal cancer patients, to examine the factors associated with CSF administration, dose reduction and mortality in the same population and to evaluate the

compliance to practice guidelines on use of CSF. This study will help to pinpoint factors associated with inappropriate CSF utilization. Targeting these factors could help decrease the inappropriate use of CSFs and may result in enhanced clinical practice, cost savings and improved outcomes.

1.6 LIMITATIONS

According to the American Cancer Society, there are no available accurate mortality statistics on colon and rectal cancers separately due to a common problem of misclassification. Often, rectal cancer mortality data are misclassified as colon cancer. The significant misclassification is likely to be due to the prevalent use of colon cancer when referring to both colon and rectal cancers while passing health information and educational messages.[3]

Both colon and rectal cancers have the same pathogenesis, risk factors and preventive measures. However, their treatment modalities differ.[23] While the focus of this thesis is specific to colorectal cancer, the epidemiology of colon cancer is inclusive of rectal. Colon cancer information found in the literature is presented here as colon cancer, while colorectal cancer information is equally presented as colorectal cancer. Both cancers are not used interchangeably in this body of work.

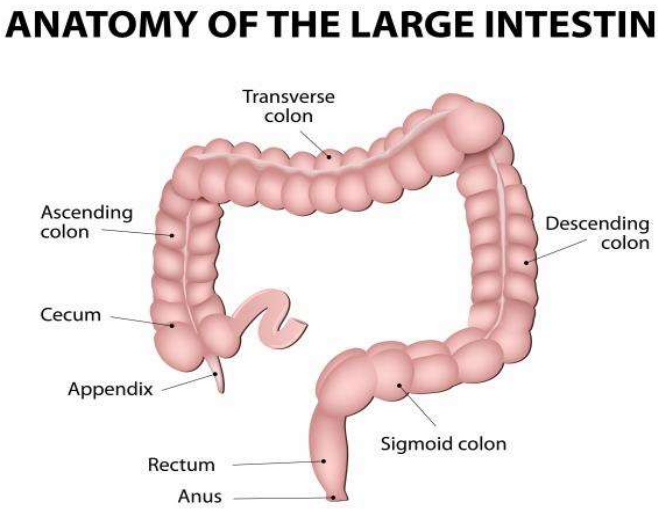
CHAPTER 2: LITERATURE REVIEW

This chapter presents a literature review for this study. The first section provides detailed information on colorectal cancer, including its epidemiology, predisposing factors, signs and symptoms, prevention, diagnosis, treatment and economic burden. The second section reviews neutropenia in detail. The next two sections present information on colony-stimulating factors (CSF) and guidelines for their use in chemotherapy, respectively. The final sections discuss the research questions, models and significance of the study.

2.1 COLORECTAL CANCER

Colorectal cancer is characterized by abnormal cell growth in the colon or rectum. The colon and rectum (colorectum) make up the large intestine, which is located in the lower part of the gastro-intestinal system. The colon is the first and larger part of the large intestine while the rectum is the smaller end part. Colorectal cancer usually begins with a polyp, which is a non-cancerous growth that forms on the inner lining of the colon or rectum and grows slowly over time. The most common growth is an adenomatous polyp, also called adenoma.[23] Metastatic cancer refers to cancer that has spread to other parts of the body other than where it started. When colon cancer spreads, it usually spreads to the liver though it could also spread to other organs in the body.

Figure 2.1: Anatomy of the Large Intestine



Source: Nordqvist C. Colorectal cancer: What you need to know. *Medical News Today* 2018; https://www.medicalnewstoday.com/articles/155598.php. Accessed May 1, 2019.[24]

2.1.1 Epidemiology

Universally, colorectal cancer is the fourth most commonly diagnosed cancer in men and third most common in women.[23] It is a major cause of morbidity and mortality, and accounts for more than 9 percent of all cancer incidence.[25] While colorectal cancer rates are rising rapidly in low and middle-income countries, rates remain high in developed countries.[26] Countries with the highest incidence rates include Australia, New Zealand, Canada and the United States.[25] Researchers estimate that the global burden of colorectal cancer will grow by 60 percent to over 2.2 million new cases and 1.1 million deaths by the year 2030.[26]

In the United States, colorectal cancer is the third most common malignancy in both men and women and the second cancer killer.[3] It is estimated that that 97,220 new cases of colon cancer and 43,030 cases of rectal cancer will be diagnosed in 2018. Though the

prevalence of colon cancer is similar in both genders, men (49,690) and women (47,530), a higher number of men (25,920) than women (17,110) will be diagnosed with rectal cancer.[1] Since the mid-1980s, colorectal cancer incidence has declined by an average of 1.6 percent per year. This decline has been attributed to a change in the forms of risk factors such as reduction in smoking, early detection and removal of precancerous polyps due to increased adherence to screening. Likewise, there has been a substantial decrease in mortality rates. Colorectal cancer death rates have been decreasing since 1980 in men and 1947 in women. The declines in mortality from 1975 to 2000 are attributed to improved treatment, changing patterns in risk factors and improved screening.[27]

In the United States, colorectal cancer prevalence is highest in African Americans and lowest among Asian and Pacific Islanders (APIs). During the time period 2009 to 2013, incidence rates in non-Hispanic blacks (NHBs) (49.2 per 100,000) were about 20 percent higher than the rates in non-Hispanic whites (NHWs) (40.2 per 100,000) and 50 percent higher than the rates in APIs (32.2 per 100,000). The disparities for mortality rates are twice that for incidence. During the time period 2010 through 2014, colorectal cancer death rates in NHBs (20.5 per 100,000) were 40 percent higher than the rates in NHWs (14.6 per 100,000) and twice the rates in APIs (10.3 per 100,000). The higher rates in NHBs are associated with unduly low socio-economic status.[28] According to the United States Census Bureau, the poverty rate in 2016 was 22 percent in blacks compared to 8.8 percent in NHWs and 10 percent in Asians.[29]

2.1.2 Predisposing Factors

Generally, the lifetime risk of developing colorectal cancer is about 1 in 22 (4.6%) for men and 1 in 24 (4.2%) for women.[30] Approximately 5 percent of Americans will develop colorectal cancer in their life time.[23] Risk of developing colorectal cancer is influenced by both modifiable and non-modifiable factors.

Some of the modifiable risk factors include physical inactivity, obesity, certain diets, certain medications, smoking and heavy alcohol use. Others include personal or family history of colorectal cancer.[30] A recent study found that combined lifestyle factors such as maintaining a healthy body weight, physical activity, limited alcohol and healthy diet reduce the risk of colorectal cancer.[31] Physical activity is strongly associated with a reduced risk of colon cancer. Studies have shown that people who involve in physical activity have a reduced risk of developing both proximal and distal tumors compared to the least active people.[32] Another study found that people who are more physically active before and after colorectal cancer diagnosis are more likely to have lower mortality rates.[33] Obesity also increases the risk of colorectal cancer, although a stronger association exists in men than in women and for colon more than rectal cancer. Compared to people who maintain a healthy body weight, obese men have a 50 percent higher risk of colon cancer, whereas obese women have a 20 percent higher risk of colon cancer. Excess body weight before diagnosis reduces the chances of survival. Smoking has also been shown to be associated with colorectal cancer and lower colorectal cancer specific survival, especially for current smokers.

Finally, persons with some medical conditions or history have an increasked risk of colorectal cancer. Individuals who have chronic inflammatory bowel disease have double the risk of colorectal cancer compared to the general population. People with Type 2 diabetes have an increased risk as well. Colorectal cancer could be hereditary as up to 30 percent of colorectal patients have a family history of the disease.[30] Non-modifiable factors that influence risk include age, sex and ethnicity. The risk of developing colorectal cancer increases with age. The median age at diagnosis for colon cancer is 68 in men and 72 in women. For rectal cancer, it is 63 years in both men and women. Due to increased rates of incidence among younger persons and declining rates in older persons, the proportion of diagnosed persons younger than 50 has increased over the years with many cases occurring in people who are in their 40s. Also, colorectal cancer incidence rates are 30 percent higher in men than in women while mortality rates are 40 percent higher. Reasons for this disparity are not completely known but could be due to differences in exposures to risk factors like cigarette smoking and sex hormones.[34] Also, incidence and mortality rates are highest in NHBs and lowest in APIs.

2.1.3 Signs and Symptoms

Early colorectal cancer presents without symptoms, but overtime as the tumor enlarges, bleeding or intestinal obstruction could occur. Sometimes the blood loss leads to anemia, causing weakness, shortness of breath and fatigue. Other symptoms that could occur include bloody stools, dark stools, change in shape of stool, constipation, decreased appetite and unintentional weight loss.

2.1.4 Diagnosis and Staging

Staging refers to the degree of cancer spread at the time of diagnosis and is important for determining possible treatments and assessing disease prognosis. The two commonly used staging systems are the TNM system and the Surveillance, Epidemiology, and End Results (SEER) staging system. While the TNM is commonly used in clinical settings, the SEER is used for descriptive and stat analysis of tumor registry data. The description of the SEER summary staging includes in situ, local, regional and distant. In in situ, cancer is confined to where it started and has not entered the wall of the colon or rectum. In local, the cancer has grown into the colon or rectum wall but has not invaded nearby tissues. Regional refers to when the cancer spreads into nearby tissues, while distant is the spread of the cancer into other body regions such as the liver.[30]

The clinical staging system commonly used is the American Joint Committee on Cancer (AJCC) TNM system. The TNM system is based on three variables: primary tumor (T), regional nodes (N) and metastasis (M) and is broadly categorized into five stages. The earliest stage is called stage O, and then there are stages I, II, III and IV. Stage II is subdivided into stage IIA and stage IIB, while stage III is subdivided into stage IIIA, IIIB and IIIC. The lower the staging number, the less the degree of cancer spread. And within a stage, an earlier letter means a lower stage. Though there are five broad stages, the TNM variables are used to further group the stages more specifically. A combination of these terms is used to determine the overall stage of a cancer patient.[35]

In addition, colorectal cancer can be described by grade, which refers to how closely cancer cells look like healthy cells when viewed with the microscope. Here the cancerous tissue is compared with a healthy tissue. Usually, healthy tissues are made up of diverse cell types. If the cancer is like healthy tissue and comprises different cell groups, it is called differentiated or low-grade tumor. On the other hand, if it is not similar to the healthy tissue, it is called poorly differentiated or high-grade tumor. The lower the tumor grade, the better the prognosis. The grades used in practice include GX, and G1 through G4, where:

- GX: The tumor grade cannot be identified;
- G1: The cells are more like healthy cells (well differentiated);
- G2: The cells are somewhat like healthy cells (moderately differentiated);
- G3: The cells look less like healthy cells (poorly differentiated); and
- G4: The cells barely look like healthy cells (undifferentiated).

2.1.5 General Cancer Classification

2.1.5.1 Histologic Classes

There are two ways cancers can be classified: (1) histologically, which is by the type of tissue in which the cancer originates and (2) by primary site, which is the location where the cancer first developed. Using the histological classification, cancer can be grouped into 6 major categories: carcinoma, sarcoma, myeloma, leukemia, lymphoma and mixed types.

Carcinoma: A carcinoma is a malignant neoplasm that arises from the epithelial tissues of the skin or a cancer of the internal or external lining in the body. Epithelial tissues are present throughout the body. The two major subtypes of carcinomas include adenocarcinoma, which develops in an organ and squamous cell carcinoma that originates in the squamous epithelium. Carcinomas account for 80 to 90 percent of all cancer cases.

Sarcoma: Sarcoma refers to cancer that originates in supportive and connective tissues such as bones, tendons, cartilage, muscle and fat. It generally occurs in young adults.

Myeloma: Myeloma is cancer that originates in the plasma cells of the bone marrow. Some proteins in the blood are produced by plasma cells.

Leukemia: Leukemias are cancers of the bone marrow. They are also liquid cancers or blood cancers. Blood cells are produced in the bone marrow. Leukemias are often characterized by overproduction of immature white blood cells which makes the patient vulnerable to infection. Leukemias are more common in children.

Lymphoma: Lymphomas are cancers that develop in the glands and nodes of the lymphatic system. The lymphatic system is a network of vessels, nodes and organs that purify fluids of the body and produce infection-fighting white blood cells or lymphocytes. Unlike leukemias that are liquid cancers, lymphomas are solid cancers. Lymphomas also occur in specific organs like breast or brain. The two categories of lymphomas are Hodgkin lymphoma and Non-Hodgkin lymphoma.

Mixed Types: Some of the mixed types of cancers may be within one category or from different categories. Examples include carcinosarcoma and adenosquamous carcinoma.[36]

2.1.5.2 Solid vs Liquid Tumors

Solid tumors are abnormal masses of tissue that usually do not contain cysts or liquid areas. Solid tumors may be benign (not cancerous) or malignant (cancerous). Leukemias (cancer of the blood) generally do not form solid tumors.[37] On the other hand, liquid tumors consist of neoplastic cells whose precursors are usually mobile.[38]

2.1.5.3 Myeloid vs Non-Myeloid Cancers

Myeloid cancers are leukemias that involve myeloid cells known as myelocytes. Non-myeloid cancers are cancers that do not involve myeloid cells (i.e., cancers other than myeloid leukemias). Non-myeloid cancers include all types of carcinoma, sarcoma, melanoma, lymphomas, lymphocytic leukemias and multiple myelomas.[39]

2.1.6 Prevention

Colorectal cancer screening can prevent cancer through early detection and removal of pre-cancerous growths. Screening detects cancer at an early stage when treatment is more likely to be successful. Thus, screening reduces cancer death by reducing incidence and increasing the chances of patient survival. The USPSTF recommends that adults age 50 to 75 be screened and screening after age 75 should be made on an individual basis.[40] Also, screening before age 50 can be done for people at increased risk due to certain factors. Both USPSTF and ACS have a number of recommended screening test options that differ

in reliability, potential harm and costs. The screening guidelines can be found in Figure 2.2 and Table 2.1 below.

Figure 2.2: USPTSF Guidelines on Colorectal Cancer Screening, 2016

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary. See the Clinical Considerations section and the Table for details about screening strategies.	A
Adults aged 76 to 85 years	The decision to screen for colorectal cancer in adults aged 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history. • Adults in this age group who have never been screened for colorectal cancer are more likely to benefit. • Screening would be most appropriate among adults who 1) are healthy enough to undergo treatment if colorectal cancer is detected and 2) do not have comorbid conditions that would significantly limit their life expectancy.	C

A: The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
C: The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.

Source: Final Recommendation Statement: Colorectal Cancer Screening. *United States Preventive Services Task Force* 2016; https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/colorectal-cancer-screening2. Accessed Feb 23, 2018.[41]

Table 2.1: ACS Guidelines on Colorectal Cancer Screening for Average and Increased Risk

Average Risk		
Starting at age 50 years, men and women should undergo one of the following screening tests: • Flexible sigmoidoscopy every 5 y • Colonoscopy every 10 y • Double-contrast barium enema every 5 y • CT colonography every 5 y • FOBT annually (take-home, multiple-sample method) • FIT annually (take-home, multiple-sample method)		
Increased Risk (due to history of polyps on prior colonoscopy)		
Risk Category	**Age/Time to Begin**	**Recommended Test(s)**
Small rectal hyperplastic polyps	Age 50 y	Colonoscopy or other screening options
1-2 tubular adenomas with low-grade dysplasia <1 cm	5-10 y after polyp removal	Colonoscopy
3-10 adenomas or adenoma >1 cm or any adenomas with high-grade dysplasia or villous features	3 y after polyp removal	Colonoscopy
>10 adenomas found on single exam	≤3 y after polyp removal	Colonoscopy
Sessile adenomas removed in pieces	2-6 mo after adenoma removal	Colonoscopy
Increased Risk (due to history of colorectal cancer)		
Risk Category	**Time to Begin**	**Recommended Test**
Colon or rectal cancer diagnosis	At time of colorectal surgery, or 3-6 mo later if metastasis absent	Colonoscopy
Colon or rectal cancer removed surgically	≤1 y after cancer resection or 1 y after colonoscopy of remaining colon	Colonoscopy repeated in 3 y; if normal, repeat every 5 y
Increased Risk (due to FH of colorectal cancer)		
Risk Category	**Age/Time to Begin**	**Recommended Test**
Colorectal cancer or adenomatous polyps in any 1st-degree relative <60 y or ≥2 1st-degree relatives at any age	Age 40 y, or 10 y before youngest immediate-family case	Colonoscopy every 5 y
Colorectal cancer or adenomatous polyps in any 1st-degree relative ≥60 y or ≥2 2nd-degree relatives at any age	Age 40 y	Colonoscopy every 10 y

Source: Colorectal Cancer Screening Guidelines Update. *US Pharmacist* 2012; https://www.uspharmacist.com/article/colorectal-cancer-screening-guidelines-update. Accessed Feb 23, 2018.[42]

There are several recommended tests for colorectal cancer screening, and each has its advantages and disadvantages. There are tests that find both polyps and cancer, and tests that find only cancer. Usually, the test a patient utilizes depends on preferences and medical condition.

2.1.6.1 Tests that Can Find both Colorectal Polyps and Cancer

i. Flexible Sigmoidoscopy: This involves an examination of the rectum and parts of the lower colon (sigmoid colon) to detect, examine and possibly remove abnormalities using a sigmoidoscope.[43] A sigmoidoscope is a flexible lighted tube with a small video camera on the end. The instrument is inserted through the anus and air is pumped into the colon for a clearer view. It is minimally invasive and usually does not require sedation. The two types of sigmoidoscopy are a flexible and rigid sigmoidoscopy. While a flexible sigmoidoscopy uses a flexible endoscope, a rigid sigmoidoscopy uses a rigid device. This is, however, not a widely used screening test in the United States. It is generally recommended to have a sigmoidoscopy every 5 years with or without Guaiac-based fecal occult blood test (gFOBT) or every 10 years with a fecal immunochemical test (FIT).[43,44]

Studies show that flexible sigmoidoscopy is associated with significant reduction in colorectal cancer incidence and mortality. People who utilize sigmoidoscopy screening after age 50 have a 60 to 70 percent lower risk of death due to colorectal cancer than those who do not get the screening.[45,46] The test identifies both cancers and precursor lesions (including polyps). If an adenoma or colorectal cancer is found, a colonoscopy would be required.

ii. Standard Colonoscopy: In this test, the physician uses a colonoscope to examine the entire length of the colon and the rectum. The colonoscope is a thin tube with a small video camera on the end and a tool for removing tissue. It is basically a longer sigmoidoscope and reaches parts of the colon a sigmoidoscope cannot reach.

During a colonoscopy, abnormal growths found in the colon and rectum are removed if necessary. Mostly, sedation is required for this test. It is recommended to have a colonoscopy every 10 years for people at average risk. Studies have shown that colonoscopy reduces mortality due to colorectal cancer.[44]

iii. Virtual Colonoscopy: This test is an advanced computed tomography. The virtual colonoscopy involves the use of a special x-ray equipment, called a computed tomography (CT) scanner to take several pictures of the colon and rectum from outside the body. A computer then assembles the pictures into detailed images, showing polyps and other abnormalities. This method is less invasive than a standard colonoscopy and does not require sedation. However, a colonoscopy is still needed to explore or remove any abnormalities found. It is recommended to have this test every 5 years. The effect of virtual colonoscopy on colorectal cancer mortality is unknown.[43,44]

iv. Double-contrast barium enema (DCBE): This test also uses a series of x-ray images to view the colon from outside the body. However, an enema with a barium solution is given to the patient prior to x-rays. If polyps or other abnormal substances are seen, then a colonoscopy is necessary to remove them. This test is not widely used in the United States because it is less sensitive compared to a colonoscopy.[43,44]

2.1.6.2 Tests that Mainly Identify Colorectal Cancer

i. Guaiac-based fecal occult blood test (gFOBT): This test detects blood in the stool using a chemical reaction. Though blood in the stool can be from cancers and

polyps, there are other possible causes such as ulcers, colitis, hemorrhoids. If FOBT is the only screening test used by an individual, it is recommended that it be done yearly.[43,44] Studies show that the gFOBT leads to a decrease in colorectal cancer mortality in people aged 50 to 80.[44]

ii. Fecal Immunochemical Test (FIT): This is also called an immunochemical fecal occult blood test (iFOBT). Like gFOBT, it tests for blood in the stool but uses antibodies to detect human hemoglobin protein.

iii. Stool DNA test (FIT-DNA): A stool DNA test tests for abnormal parts of DNA from cancer or polyp cells. Colorectal cancer cells usually have DNA mutations in certain genes which are detected by the FIT-DNA. The only FDA approved stool DNA test is Cologuard.

Usually, the test a patient utilizes depends on factors such as age, family history, convenience, preferences and medical condition.[43,44]

2.1.7 Treatment

Colorectal cancer treatment depends on the size, location and spread of the tumor. Treatments could be local or systemic. Local treatments are therapies that treat the cancer without affecting the rest of the body. They include surgery, radiation therapy and ablation. Systemic treatments are therapies that reach cancer cells anywhere in the body. They include chemotherapy, targeted therapy and immunotherapy.

2.1.7.1 Local Therapies

a. Surgery

Surgery is the primary treatment for early stage colon cancers. The type of surgery depends on the extent of the cancer. Some of the surgical options include polypectomy, colectomy and colostomy.

i. Polypectomy: In a polypectomy, the cancer is removed as part of the polyp by passing a wire loop through the colonoscope to cut the polyp from the colon. A local excision is used to remove superficial cancers from the colon wall.

ii. Colectomy: A colectomy is a surgery that removes all or part of the colon as well as nearby lymph nodes. If only part of the colon is removed, it is called a hemicolectomy or partial colectomy. If all of the colon is removed, it is called total colectomy. This is usually only performed if there is disease in part of the colon without the cancer. A colectomy can be done in two ways: open colectomy or laparoscopic colectomy. In open colectomy, a single incision is made in the abdomen while laparoscopic colectomy uses several smaller incisions and a laparoscope. A laparoscope is a thin lighted tube with a small video camera used to view the abdomen.[47]

iii. Colostomy: A colostomy is a procedure that involves the use of a surgical opening or stoma which is attached to the top end of the colon to provide a path for waste (stool) to exit the body into a waste pouch worn by the patient.

Side Effects of Colon Surgery

In general, the side effects of surgery include pain and tenderness in the site of the surgery or in stoma, constipation or diarrhea. Another possible side effect is developing scar tissue in the abdomen known as adhesions. This causes organs and tissues to stick and could lead to bowel blockade, requiring further surgery.[47,48]

b. Radiation therapy

Radiation therapy uses high energy X-rays to destroy cancer cells. It is not commonly used for colon cancer but may be used to treat cancers that have spread to other areas or control cancers in patients who are not healthy enough for surgery. It can also be used to palliate symptoms in advanced cancer patients and post-surgery to destroy any cancer cells that remain. The three main types of radiation include external beam radiation therapy, internal radiation and radioembolization.

i. External beam radiation therapy is more commonly used for colorectal cancer patients. Here the radiation is beamed on the cancer from a machine outside the body.

ii. The internal radiation therapy is usually used to treat rectal cancers and involves putting a radioactive substance inside the rectum or close to the tumor with the advantage of not having to pass the skin.[47] Other types of radiation therapy are techniques that can be used to rid the body of cancers not removable via surgery. For instance, intraoperative radiation is the use of a high single dose of radiation which is administered via surgery. Brachytherapy uses radioactive seeds that can be injected into a body organ when surgery is not an option.[48]

iii. Radioembolization is the administration of radiation during an embolization procedure.

Side Effects of Radiation

Possible side effects of radiation therapy include skin irritation (redness, peeling) at radiation sites, nausea, rectal irritation, bowel incontinence (stool leak), bladder irritation, burning while urinating, blood in urine and bloody stools. Also, sexual problems such as infertility could occur in both men and women.[47,48]

c. Ablation

This is often treatment options for people whose cancers cannot be cured with surgery or when the cancer has spread to other organs. Ablation destroys tumors without removing them from the body. The types of ablation include radiofrequency ablation, ethanol ablation and cryosurgery. Radiofrequency ablation uses high energy radio waves to destroy tumors. Ethanol ablation is the use of concentrated alcohol injections to destroy cancer cells. Cryosurgery is the freezing of a tumor with a thin metal probe and extremely cold gasses.

d. Embolization

This is a procedure that involves the injecting of substances into the body to hinder blood flow to cancer cells in the liver. It is often used for tumors that are too large to be treated with ablation. The three embolization options include arterial, chemo and radio embolization. Arterial embolization is the use of a catheter to inject small particles into an artery to plug it up. Chemoembolization is a combination of chemotherapy and embolization. It is done by giving chemotherapy through the catheter directly into the

artery, then plugging up the artery. Radioembolization is a combination of embolization and radiation. This is done by injecting small beads coated with a radioactive substance into the hepatic artery.

Side Effects of Embolization

Side effects of embolization procedures include belly pain, fever, nausea, liver infection and gallbladder inflammation. Also, liver function could worsen because sometimes healthy cells are affected in embolization.

2.1.7.2 Systemic Therapies

a. Immunotherapy

This is the use of medicines to aid the immune system to recognize and destroy cancer cells. It is used to treat advanced colorectal cancer. The immune system has the ability to not destroy healthy body tissue. It uses checkpoint proteins on immune cells to do this. Immune checkpoint inhibitors (e.g., pembrolizumab and nivolumab) are drugs that target and block these checkpoints, thereby boosting immune system response against cancer cells to slow their growth.[49]

b. Targeted therapy

In targeted therapy, specific genes and proteins that contribute to cancer growth and survival are targeted and their growth and spread blocked. They can be used alone or along with chemotherapy and do have less side effects. Some types include Vascular Endothelial Growth Factor Inhibitor (VEGF) inhibitors, and Epidermal Growth Factor Receptor (EGFR) Inhibitors.

i. VEGF Inhibitors: These inhibit VEGF function, which is to help tumors form new blood vessels – a process called anti-angiogenesis. Anti-angiogenesis therapies hinder angiogenesis and include bevacizumab (Avastin) which has been approved as first line treatment for advanced colorectal cancer, regorafenib (Stivarga), ziv-aflibercept (Zaltrap) and ramucicumab (Cyramza).

ii. EGFR Inhibitors: EGFR inhibitors block EGFR which slows the growth of cancer. Examples of drugs here include cetuximab and panitumumab.[48,49]

c. Chemotherapy

Chemotherapy involves use of anticancer drugs to destroy cancer cells. It can be administered systemically or regionally. In systemic chemotherapy, drugs are injected into a vein or administered by mouth to reach cancer cells throughout the body. In regional chemotherapy, drugs are directly injected into an artery that leads to the tumor. The regional method has less side effects because a limited amount of drug is reaching the rest of the body. For instance, chemotherapy can be directly injected into the hepatic artery (hepatic artery infusion) for a cancer in the liver. Chemotherapy is usually given in cycles, with each cycle lasting about 2 to 4 weeks. Each period of treatment is followed by a rest period to enable recovery of the body. Chemotherapy can be administered at different times during treatment such as:

i. Adjuvant chemotherapy: Adjuvant refers to therapy given in addition to the main treatment to maximize effectiveness. Adjuvant chemotherapy is given post-surgery to destroy cancer cells that were not destroyed during surgery due to their small sizes or having settled in other parts of the body away

from the main tumor. Adjuvant therapy reduces the chances of cancer recurrence.

ii. Neoadjuvant chemotherapy: This refers to therapy given before the main treatment. Chemotherapy could also be given before surgery to shrink the cancer and make surgery easier. Neoadjuvant chemotherapy is often done in rectal cancer.

For advanced cancers that have spread to other parts of the body, chemotherapy is given to shrink tumors and for palliative purposes. Though this would not likely cure the cancer, it can help the patient live longer. Some of the drugs used for chemotherapy could be given singly or as a combination of drugs. Chemotherapy drugs could also be combined with drugs used for targeted therapy. Some of the drugs used in chemotherapy include 5 fluorouracil (5-FU), leucovorin or levo-leucovorin, capecitabine (Xeloda), irinotecan (Camptosar), oxaliplatin (Eloxatan), trifluridine and tipiracil (Lonsurf).[50]

Side Effects of Chemotherapy

Drugs used in chemotherapy function by attacking quickly dividing cells in the body such as cancer cells. Unfortunately, some normal body cells that are quickly dividing get attacked in the process, leading to side effects. Some of the common side effects are hair loss, mouth sores, loss of appetite, diarrhea, nausea, vomiting, fatigue, increased chance of infections due to low white blood cells, easy bleeding due to low platelets and fatigue due to low red blood cells. Additionally, some side effects are specific to certain drugs. For instance, hand foot syndrome is common with capecitabine or 5-FU. Neuropathy (nerve damage) is common with oxaliplatin. Allergic reactions are also common with

oxaliplatin while diarrhea, though a common side effect with most of the drugs, is worse with irinotecan.[48,50]

2.1.7.3 Treatment Options by Stage

Generally, Stages 0, I, II and III of colon cancer are curable with surgery, but usually with stage III and sometimes with stage II, patients receive chemotherapy after surgery to increase the likelihood of eliminating the cancer. Stage IV is often not curable, but tumor growth and symptoms can be managed. For stage 0 colorectal cancer, the treatment is a polypectomy (removal of a polyp) during a colonoscopy. For stage I, a surgery could be done to remove tumor and lymph nodes. For stage II, surgery is also the first line of treatment, and it is sometimes combined with adjuvant chemotherapy. Treatment for stage III also involves surgery and sometimes adjuvant chemotherapy. For stage IV (metastatic colon cancer), the treatment could include a combination of surgery, radiation therapy, immunotherapy and chemotherapy to slow the spread of the cancer and also to shrink the tumors. The goal of surgery here is to relieve blockage of the colon and prevent local complications. A resection can also be done, which is a surgery to remove parts of other organs that contain cancer in them.

2.1.7.4 Remission and Recurrence

A remission occurs when the cancer can no longer be detected in the body, also known as having 'no evidence of disease,' or NED. Remission could be partial or complete. In partial remission, some of the cancer remains but the tumor is smaller, and the patient can stop treatment. In complete remission, the cancer as well as symptoms cannot be

detected or measured. Complete remission is usually referred to as NED but does not mean the cancer is cured. Also, remissions can be temporary or permanent. However, after five years, the cancer can be said to have been successfully managed.

Recurrence refers to a cancer that returns after the patient has been in remission. This could happen because cancer cells could remain unnoticed in the body for years following treatment. If the cancer returns in the same site as before, it is called a local recurrence. If cancer returns to a surrounding organ, it is called a regional recurrence and if in another place, it is called a distant recurrence. Treatment outcomes usually vary widely, but if the cancer cannot be cured or controlled, it is referred to as advanced or terminal cancer.[48,51]

2.1.8 Economic Burden

Colorectal cancer imposes a significant economic burden on the society. A study that estimated the economic burden of colon cancer hospitalizations using hospital discharge data found that the mean total hospital charges were $4.57 billion per year.[52] Another study estimated annual expenditures for colorectal cancer to be $5.3 billion in 2000, inclusive of both direct and indirect costs.[6]

The total costs of colorectal cancer in 2010 was estimated to be $14.1 billion, second only to breast cancer. Amongst cancers, colorectal cancer has the third highest mortality costs associated with premature deaths from cancer.[53] A study by Zheng et al. used Medical Expenditures Panel Survey (MEPS) data to measure excess economic burden attributable to colorectal cancer patients. They found that colorectal cancer survivors

experience statistically significant higher economic burden compared to individuals without a cancer history ($P<0.001$).[54] The results were significant for both the elderly and non-elderly population.

2.1.9 Survival

Survival for colorectal cancer usually depends on stage of disease at diagnosis. The relative survival rate is 65 percent at 5 years after diagnosis and 58 percent at 10 years. By site of disease, survival rate ranges from 90 percent 5-year survival rates for localized stage cancers, 70 percent for regional, 10 to 14 percent for metastatic cancers.[25,30] Overall 5-year survival rates are slightly higher for patients with rectal tumors (67%) than for those with colon tumors (64%). Based on tumor location, 5-year survival is higher for patients with distal tumors (69%) than for those with proximal tumors (65%). Younger patients also have higher survival. The 5-year survival is 69 percent in those younger than 65 and 62 percent in those aged 65 years and more.[55] Generally, the earlier the stage at diagnosis, the higher the chances of patient survival.[25]

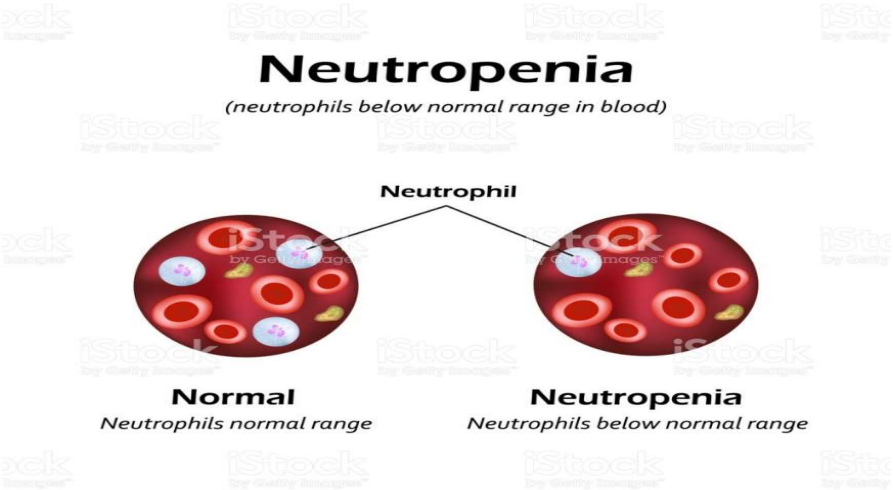
The survival for colorectal cancer at all stages have improved significantly since the 1960s. Also, survival rates over time have been better in countries with higher life expectancy and access to care. And increase in survival rates was higher for whites compared to non-whites. Disparities in colorectal cancer survival exist both globally and in the United States. Most of the global and regional disparities is likely due to differences in access to care.[25] In the United States, blacks and American Indians/Alaska Natives (AI/AN) have the lowest survival rates for every stage. AIs/ANs are least likely to have a

localized stage diagnosis and most likely, together with blacks, to have a distant-stage diagnosis. These disparities are attributable to unequal socioeconomic status that results in differences in access to early detection and timely and high-quality treatment.[30] As of January 2016, there were 1.5 million Americans alive with a history of colorectal cancer.[55]

2.2 NEUTROPENIA

Neutropenia is a condition in which the number of neutrophils in the blood is significantly reduced, affecting the ability of the body to fight infections.[56] The two most common blood cells are the red blood cells and the white blood cells. The function of the red blood cell is oxygen transport from the lungs to other parts of the body while the primary function of the white blood cell is to protect the body from infection.[57] The five major types of circulating white blood cells include basophils, eosinophils, lymphocytes, monocytes and neutrophils.[56] Of these, the most common types are the neutrophils and lymphocytes. While lymphocytes protect the body against viruses, neutrophils defend the body against bacteria. Neutropenia is a situation in which the number of neutrophils in the body is too low. Since neutrophils are essential in protecting the body against bacterial infections, a patient with neutropenia remains susceptible to bacterial infections.[57]

Figure 2.3: Neutropenia



Source: https://www.healthnavigator.org.nz/health-a-z/n/neutropenia/

Clinically, neutropenia is said to occur when the absolute neutrophil count (ANC) is less than 1500 per microliter (1500/µL).[56] Generally, the blood of a healthy adult contains about 1500 – 7000 neutrophils/µL.[57] The ANC is calculated by multiplying the total white blood cells by the portion of neutrophils among the white blood cells as determined by white blood cell differential analysis. Other factors such as age, race, genetics and environmental factors can affect neutrophil count. For instance, blacks may have a lower ANC value of 1000 cells/µL with a normal total white blood cell count. Based on the ANC, neutropenia may be classified as mild, moderate or severe. Neutropenia is said to be mild when the ANC ranges 1000 – 1500/µL, neutropenia is moderate when the ANC ranges 500 – 1000/µL and severe neutropenia occurs when the ANC is less than 500/µL.[58]

A number of medical terms are sometimes used interchangeably with neutropenia, even though their exact definitions differ. Leukopenia is a decreased number of white blood cells in general, while granulocytopenia is a reduced number of all granulocyte type blood cells which include neutrophils, eosinophils, and basophils. Given that neutrophils are the most numerous among the granulocytes, granulocytopenia is sometimes used to refer to neutropenia. On the other hand, agranulocytosis refers to a total absence of all granulocytes. And this is also sometimes used interchangeably with severe neutropenia.[56] It usually refers to cases where the ANC is less than than 100/µL.[58]

2.2.1 Pathophysiology

Neutrophils are made in the bone marrow and released into the bloodstream. Most neutrophils in the body are contained in the bone marrow. The entire neutrophil content in the body can be divided into 3 sections: the bone marrow, the blood and the tissues. In the bone marrow, neutrophils could exist in two divisions: the mitotic section and the maturation-storage section. Neutrophils exit the marrow storage section and enter the blood without going back to the marrow. Then they leave the blood randomly after 6 – 8 hours and enter the tissues where they are destined for cellular action or death.[58] The mature neutrophil has a lifespan of about 3 days.[56]

Neutropenia is associated with an increased risk of bacterial infections in patients, and the risk depends on its cause and severity. Generally, infection risk increases as ANC decreases. The duration and severity of neutropenia is directly correlated with total incidence of all infections and life-threatening infections. When the ANC is consistently

lower than 100 cells/μL for longer than 3-4 weeks, then incidence of infection gets closer to 100 percent. At this point, life threatening infections and sepsis could occur.[58]

2.2.2 Etiology

The etiology of neutropenia could be categorized via mechanism or etiology. The mechanism that lead to neutropenia are not well understood. Usually neutropenia happens after a long-term exposure to some medication or other substances which results in decreased neutrophils produced by the bone marrow. In other instances, a repeated but intermittent drug is required though the exact exposure as related to neutropenia is unknown.

On the other hand, categorization via etiology is grouped as either congenital or acquired. Congenital neutropenia is hereditary and most occur due to mutations in the gene encoding neutrophil elastase, ELA2. The acquired neutropenia are mostly related to any of three broad categories: autoimmune, infection and drugs. Chronic benign neutropenia (also called chronic idiopathic neutropenia) is an overlap disorder with both hereditary and acquired forms.

2.2.2.1 Congenital Neutropenia

Congenital neutropenia with associated immune defects occurs when an individual has neutropenia with abnormal immunoglobulins. Congenital or chronic neutropenia is caused by a recessive gene and is often recognized at birth or shortly afterwards. Cyclic neutropenia is characterized by sessions of neutropenia and infection usually in infants or children. Chronic benign neutropenia usually occurs with overall low risk of infection.

Chronic idiopathic severe neutropenia can occur in both children and adults and is a diagnosis of exclusion. Neutropenia associated with phenotypic abnormalities include Schwachman syndrome, Barth syndrome and Chediak-Higashi syndrome. Other congenital neutropenia includes lazy leukocyte syndrome which is a severe neutropenia with associated abnormal neutrophil motility and myelokathexis that is characterized by moderate neutropenia and recurrent infections and usually presents in infancy.

2.2.2.2 Acquired Neutropenia

Acquired neutropenia can be caused by intrinsic bone marrow disease, infection, nutritional deficiency, drugs and chemicals, or could be immune mediated.

i. Bone marrow disease: Inherent bone marrow sicknesses that could lead to neutropenia include aplastic anemia, ionizing radiation, tumor infiltration, myelofibrosis, granulomatous infection and hematologic malignancies such as leukemia, lymphoma and myeloma.

ii. Immune-mediated: Immune-mediated neutropenia could be caused by drugs (e.g., quinidine, penicillins, sulfonamides, cephalosporins) that induce antibody formation in the body. These antibodies destroy granulocytes and the drug could form immune complexes that attach to neutrophils.

    In autoimmune neutropenia, the body makes antibodies to destroy neutrophils and could be associated with the following diseases: Crohn's disease, rheumatoid arthritis, Hodgkin lymphoma, chronic autoimmune hepatitis, systemic lupus erythematosus and pure red blood cell aplasia.

iii. Infection-related: The most common form of acquired neutropenia is via infection. Some of the infections that could cause neutropenia include bacterial sepsis, typhoid, tuberculosis, malaria, dengue fever and viral infections such as influenza, measles and viral hepatitis.

iv. Nutritional deficiency: Some of the nutritional deficiencies that could cause neutropenia consist of Vitamin B12, folate and copper deficiencies.

v. Drugs and Chemicals (apart from cytotoxic chemo): Several drugs have been associated with neutropenia with the greatest risk being with antithyroid medications, macrolides and procainamides. Some drugs could cause neutropenia by acting via an immune-mediated mechanism while other drugs have direct harmful effects on the bone marrow cells or on neutrophil precursors in the mitotic compartment. In addition, other drugs could have a combination of immune and nonimmune mechanisms or could have mechanisms of action that are not known.

   Drug and chemical exposure most commonly leads to agranulocytosis. Drugs that cause bone marrow depression or aplasia are capable of causing agranulocytosis. Some of the drugs frequently associated with agranulocytosis include phenothiazine, antithyroids, sulfonamides, aminopyrine and chloramphenicol.

vi. Miscellaneous Immunologic-related: Immunologic neutropenia could occur after a bone marrow transplantation and blood product transfusions.[58]

vii. Cytotoxic chemotherapy: Neutropenia could occur as a side effect of chemotherapy. This happens when myelosuppressive chemotherapeutic treatment reduces the ANC.[59]

2.2.3 Chemotherapy Induced Neutropenia

Chemotherapy and radiotherapy are known to be major causes of neutropenia and febrile neutropenia.[60] Neutropenia is a common toxicity of chemotherapy caused by bone marrow suppression. Chemotherapeutic drugs work by destroying rapidly growing cells, which is a characteristic of cancer cells. However, it also affects normal cells that grow rapidly in various parts of the body such as bone marrow, hair follicles, mouth, etc. Furthermore, chemotherapy drugs affect the production of folic acid as well as the synthesis of DNA, RNA and protein by acting as antimetabolites, causing bone marrow destruction. Some drugs that are highly associated with neutropenia include asparaginase, cytarabine, cisplatin, busulfan and methotrexate. Some studies have found a significant relationship between neutropenia and chemotherapy drugs. Buffoni et al. found that the combination of chemotherapy drugs cisplatin and vinorelbine, though highly effective, was associated with febrile neutropenia which was fatal in some of the study subjects.[61] Likewise, Banerji et al. found the combination of chemotherapy drugs etoposide and carboplatin to be significantly associated with neutropenia.[62] However, different chemotherapy regimens are not associated with the same severity of neutropenia. Research suggests that neutropenia is associated with the regimen intensity.[63] While high or intensive chemotherapy medications may lead to neutropenia or even severe neutropenia, low

chemotherapy doses may cause other adverse effects such as nausea, alopecia, thrombocytopenia, anemia and vomiting.[60,64]

Chemotherapy administration could follow either of two routes: systematic which includes intravenous (IV), oral and intramuscular (IM) or local which includes intrathecal, intraperitoneal, intra-arterial and intrapleural. Of these, IV and oral are most commonly used. This is due to the advantage of the drug reaching tumor cells throughout the body. These routes (IV and oral) also have the disadvantage of reaching and destroying other body tissues, hence causing increased side effects. Therefore, the primary goal of IV chemotherapy is to achieve a systematic concentration that is effective for the cancer.[60]

Chemotherapy induced neutropenia usually occurs 3 to 7 days after administration of chemotherapy and continues until ANC levels return to normal. The chemotherapy regimen affects how the neutrophil count drops and length of the illness and recovery. Chemotherapy induced neutropenia increases the risk of life threatening infections in a patient and could disrupt chemotherapy. This disruption in chemotherapy could reduce the chances of a patient's cure or survival. However, neutropenia could be prevented via use of certain medications.[65]

2.2.4 Epidemiology

The average incidence of neutropenia in the United States is 56.4 per million people. Generally, neutropenia occurs in 1 out of 3 patients treated with chemotherapy. There are very few studies that give an exact number on neutropenia prevalence.[60] The estimated frequency of agranulocytosis is 1.0 – 3.4 cases per million persons per year.

There is a higher incidence of neutropenia in the elderly compared to younger individuals. However, agranulocytosis occurs across all ages. Neutropenia occurs more frequently in women than in men. However, agranulocytosis occurs slightly more frequently in women than men. Blacks, Ethiopians and certain populations could have lower ANCs as a result of lower white blood cell counts. Analyses from the National Health and Nutritional examination survey showed the prevalence of neutropenia to be 4.5 percent among blacks, 0.79 percent in whites and 0.38 percent in Mexican-Americans.[58]

Studies show that neutropenia is associated with solid tumors particularly breast cancer, as 25 percent of breast cancer patients develop neutropenia. Of patients with solid tumors, breast cancer patients have the highest risk for developing severe neutropenia and febrile neutropenia during their first cycle of chemotherapy.[60]

2.2.5 Predisposing Factors

The risk factors for neutropenia include patient-related, treatment-related and disease-related factors. Among the patient-related factors, being female is a risk factor for neutropenia. A systematic review of risk factors for febrile neutropenia showed female gender to be a risk factor for developing febrile neutropenia or being hospitalized for febrile neutropenia.[66] In another study, gender was found to be significantly associated with neutropenia severity as well as neutropenia complications.[67]

Also, neutropenia is more common among individuals aged 50 years or older. Compared to young people, older individuals are less able to produce mature neutrophil cells due to age. The systematic review by Lyman et al. found age to be a risk factor for

febrile neutropenia, as well as febrile neutropenia related hospitalizations.[66] Ethnicity has been linked to neutropenia. Hershman et al. found an association between ethnicity and neutropenia among cancer survivors with white blood cell levels in African American women being significantly lower than among white women.[68] Similarly, studies demonstrate that comorbid conditions with cancer is a risk factor for febrile neutropenia. The risk of febrile neutropenia increases in direct proportion to the number of comorbidities a patient has. [69,70]

The treatment-related factors include chemotherapy regimen and prophylaxis for neutropenia. Several studies suggest that certain chemotherapy regimen and dose intensity of the regimen are significant predictors of febrile neutropenia and febrile-neutropenia related hospitalization,[71-73] especially given that some chemotherapy medications are more myelosuppressive than others. On the other hand, patients who receive primary prophylaxis with G-CSF have been shown to be at a lower risk of febrile neutropenia and related hospitalizations, and this holds across various forms of cancers.[15,71,72]

For the disease-related factors, the type of tumor, having an advanced disease as well as genetic factors have been pinpointed as risk factors for neutropenia.[66]

2.2.6 Signs and Symptoms

Neutropenia itself does not present with symptoms but leads to an increased susceptibility to infections in individuals. The symptoms noted are often symptoms of an infection or the underlying cause of the neutropenia. Usually, patients who undergo chemotherapy are at an increased risk and therefore undergo routine blood tests to test for

neutropenia. The infections can appear as ulcers, rashes and abscesses. In most patients, fever is the only symptom. Other signs of an infection include high fever, malaise, flu-like symptoms, abdominal pain, diarrhea and vomiting, sore throat, mouth sores, coughing, increased urination and troubled breathing.[13]

2.2.7 Diagnosis

Neutropenia is diagnosed using a complete blood count test. The complete blood count involves measuring the amount of neutrophil in the blood. If the neutrophil count is low, tests may be repeated to be certain. Following the blood test, a bone exam (bone marrow aspirate) may be carried out to confirm presence of neutropenia. This involves obtaining bone marrow aspirates from for a bone biopsy.[60] It can also diagnosed via cytogenetic evaluation and molecular testing.[57]

2.2.8 Management

2.2.8.1 Prevention

With certain chemotherapy regimens, preventing neutropenia is difficult or even impossible. However, some measures can be taken to help prevent or reduce the duration or severity of neutropenia. Generally, in cancer patients, neutropenia is managed by chemotherapy dose reduction, dose interval delays, initiation of primary or secondary prophylaxis using hematopoietic growth factors, also called recombinant granulocyte colony-stimulating factors (G-CSF), based on individual febrile neutropenia risk assessment and chemotherapy regimen.[74]

i. Chemotherapy dose modification: Reducing the dose of chemotherapy could help reduce neutropenia. The disadvantage of dose reduction is that it affects the dose-response relationship of the drug. While decreasing doses may prevent neutropenia, drug efficacy may also be decreased. This option is most relevant for patients on palliative care, not curative treatment. Also, dose intervals can be delayed or modified.[75]

ii. Growth Factors (Primary prophylaxis): Primary prophylaxis using G-CSFs can be initiated. The oldest G-CSF is filgastrim, while a longer acting one is pegfilgastrim. However, patients must be individually and appropriately selected based on risk assessment of febrile neutropenia and chemotherapy regimen.[74] The ASCO has published guidelines on use of these growth factors based on patient risk level. There is evidence that CSFs can prevent up to 50 percent of neutropenic fevers.[76-78] Studies have shown that the risk of febrile neutropenia is highest at the first cycles of chemotherapy.[79,80]

iii. Growth Factors (Secondary Prophylaxis): Patients with neutropenic fever are at a higher risk to develop it again in subsequent therapy. Usually, secondary prophylaxis is administered especially if dose reduction is unfavorable for the patient.[75]

iv. Antibiotics: Prophylactic antibiotic therapy can be administered. However, there is a possibility of developing resistance to antibiotics.[75] But a combination of neutropenia and having a gram negative bacterial infection is associated with a high mortality. Therefore, antimicrobial therapy must be started as a mono antibiotic

therapy or combination therapy. Empirical antibiotics used must be broad spectrum to cover most potential pathogens. The three widely used antimicrobial strategies for treating febrile neutropenia include: (1) a combination of beta-lactam with aminoglycoside; (2) monotherapy with a wide range beta-lactam; and (3) both strategies combined. Generally, several antibiotics may be used to treat neutropenia. Though, only a few of them are effective in the treatment of febrile neutropenia. For instance, ceftazidime is one of the most effective antibiotics and is approved for the treatment of febrile neutropenia in patients of different ages.

v. Other therapies: Antifungal and antiviral drugs can also be administered during treatment depending on type of microbial infection. Neutropenia is associated with infections which can be bacterial, fungal or viral in origin.[60]

2.2.8.2 Treatment

When neutropenia is associated with fever, it is called febrile neutropenia. When this occurs, treatment is necessary due to an increased inability of the body to fight infections. Hospitalization and administration of broad spectrum antibiotics are necessary until the patient recovers an adequate neutrophil count.[74]

2.2.9 Prognosis

The prognosis of neutropenia depends on the cause, duration and severity of the neutropenia. Due to improved care and improved broad-spectrum antibiotic agents, the prognosis for patients with neutropenia has improved. However, patient survival depends on recovering a sufficient number of neutrophils. Deaths related to neutropenia often

involve infections during severe episodes of neutropenia and usually correlate with duration and severity of neutropenia. Severe medical complications occur in about 21 percent of patients who have cancer and neutropenia.[81-83] Three known high-risk subgroups of cancer patients with febrile neutropenia include: inpatients with fever while developing neutropenia, outpatients who require acute care and stable outpatients with uncontrolled cancer.

Drug induced agranulocytosis has a mortality rate of 6-10 percent. Untreated agranulocytosis causes a high risk of mortality but prompt treatment leads to an improved prognosis.[58]

2.2.10 Economic Burden

Neutropenia as well as febrile neutropenia impose an economic burden on patients and society. Previous studies estimate that each year in the United States, over 60,000 cancer patients are hospitalized due to neutropenia, of which 4,000 die of febrile neutropenia.[84] Tai et al.'s 2012 study using a nationally representative sample showed that 91,560 adults and 16,859 children were hospitalized due to neutropenia. The total cost for hospitalizations for adults was $2.3 billion, and $439 million for children, which represents 8 percent and 27 percent of all cancer-related hospital costs for adults and children, respectively. Adult cancer patients who were hospitalized for neutropenia stayed longer on average and paid about $5700 more than adult cancer patients who were hospitalized for other reasons. Individuals who were hospitalized for neutropenia were more likely to be admitted via the emergency room than individuals who were treated for other reasons.[85]

One study that assessed the economic burden of colorectal cancer patients with febrile neutropenia showed a mean hospitalization cost of $19,667 in 2010.[86]

2.3 Febrile Neutropenia

Febrile neutropenia refers to neutropenia with fever. It is characterized by a decrease in body neutrophil count below 500cells/mm^3 and the occurrence of fever.[87] Fever is defined as a rise in auxiliary temperature (>=38.5C) sustained for at least 1 hour.[88] It is a usual occurrence in cancer patients due to their chemotherapy regimens. Neutropenic fever is typically associated with infections caused by microorganisms including bacteria, fungi and viruses. However, severe infections are most commonly seen with gram negative bacteria although gram positive bacteria can cause life threatening infections as well.

Though any type of neutropenia can become febrile, it is most common in cancer patients undergoing therapy. Thus, cancer patients are routinely screened for febrile neutropenia. It is diagnosed by a physical examination for fever and a complete blood count test for neutropenia.[87]

2.3.1 Epidemiology

The incidence of febrile neutropenia in the United States is estimated to be 60,294 per year including 7.83 cases per 1000 cancer patients. However, the incidence is higher (43.3 cases per 1000 individuals) in persons who suffer hematological malignant tumors. Incidence of febrile neutropenia varies depending on cancer type, chemotherapy regimen, age, sex and antibiotic treatment.[87]

Over the years, the morbidity and mortality rates of febrile neutropenia have decreased due to appropriate treatment, care and preventive measures. Fifty percent of mortality in patients receiving chemotherapy for solid tumors has been attributed to febrile neutropenia. Also, in patients receiving chemotherapy for acute leukemia, febrile neutropenia related infections cause 50 percent to 75 percent of deaths. The rapid and effective use of antibiotics has reduced associated mortality to 10 percent. In the United States, mortality rates of 6.8 percent to 9.5 percent have been reported. In patients with solid tumors and hematological malignancies, mortality rates are at 5 percent and 11 percent, respectively. Mortality rates increase to 15 percent in patients with gram-negative bacteria, whereas gram-positive bacteria account for 5 percent. Elderly patients are at a higher risk of febrile neutropenia and have higher morbidity and mortality.[87]

2.3.2 Consequences

Febrile neutropenia is often associated with complicated infections and is seen as an oncologic emergency. It poses a significant threat to patient survival and this threat is worsened if there is a persistent occurrence of antibiotic resistant microorganisms which causes infections that are difficult to manage. The most serious infections are associated with gram-negative bacteria and are usually life-threatening. However, other infections caused by gram-positive bacteria, as well as viral and fungal infections can be dangerous and can lead to significant morbidity and possibly mortality. In patients with neutropenia without fever, neutropenia leads to chemotherapy delays, and/or dose modifications which can affect patient outcomes and survival.

Neutropenic colitis, also known as typhlitis is another serious complication of neutropenia. It is characterized by fever and abdominal pain. It is more common in hematological malignancies and are often treated with antibiotics. Sometimes, acute surgery may be required if there is concern for the ischemic bowel.[74]

2.3.3 Risk Assessment

The risk of developing fever is the most important factor that determines how CSFs will be used.[89] It is recommended that the physician assesses the patient's risk at the start of chemotherapy, by determining their regimen and individual risk factors.[90] Patients with neutropenia can be categorized based on risk of complications into three categories: high risk (>20%), intermediate risk (10-20%) or low risk (<10%). The risk assessment is used to develop a management plan for patients. The National Comprehensive Cancer Network (NCCN) and other bodies have issued guidelines for the stratification of risk of febrile neutropenia.[87] The Multinational Association of Supportive Cancer (MASCC) risk index score is a validated tool that can be used to predict patient risk of developing complications. The tool consists of 8 items that can be assessed to assign risk. Patients with a score of 21 or more are considered low risk while patients with lower scores are considered high risk and require more intensive management. Although there are other tools in use for the same purpose, the MASCC tool has been externally validated.[74]

2.4 COLONY-STIMULATING FACTORS (CSFS)

CSFs are medications that help the body produce white blood cells. They are glycoproteins produced by the body as well as made in the laboratory. They are also called

white blood cell growth factors or hematopoietic (blood-forming) growth factors. Cancer patients undergoing chemotherapy usually have low numbers of white blood cells as a result of cancer drugs which increase the risk of infections. White blood cells are used by the body to fight infections but are destroyed in cancer treatment, leading to neutropenia or febrile neutropenia.

CSFs are supportive drugs. They are not effective on cancer cells and therefore do not cure cancer. Rather they are used to prevent or lessen infections by stimulating the bone marrow, leading to an increased production of blood cells which strengthens the immune system. They are given as injections, usually 24 hours after a chemotherapy treatment.[16]

2.4.1 Biology

CSFs regulate granulocytes and macrophages in the body. Granulocytes and macrophages are part of the immune system and protect the body against infections. Mostly, these cells have a short life and need to be continually replaced by new cells. As long as the individual remains in good health, the cell numbers remain constant. However, the body produces these cells in response to demand. In the presence of an infection, production of granulocytes and macrophages can be highly increased. The flexibility to respond to urgent demands by the body requires a highly responsive control system. CSFs, in a group of 4 glycoproteins, help the body achieve the competing demands for stability and flexibility in cell production. The CSFs belong to a group of regulatory factors known as cytokines. Sometimes the CSFs interact with other cytokines synergistically in the

control system. Also they can interact with some bone marrow cells in the control of the formation of stem cells which are early precursors of granulocytes and macrophages.[17]

2.4.2 Actions

The CSFs are glycoproteins with molecular weight ranging from 18 to 70,000. They have a short half-life of a few hours in vivo and can be produced either locally at the site of infection or systemically by multiple tissues. The CSF control system responds promptly to changing demands. The five major actions of CSFs on responding granulocyte-macrophage cells include: (1) preventing cell death by blocking apoptosis; (2) stimulating cell division in a dose-response manner which determines cell count; (3) influencing the lineage-commitment choices of cells; (4) initiating and maintaining cell maturation; and (5) stimulating the actions and functions of mature end cells.[17]

In addition, the CSFs have an influence on all bone-marrow derived cells such as erythrocytes, monocytes, Langerhans cells, megakaryocytes, lymphocytes, eosinophils and mast cells. These cells require such interactions to be fully mature and functional. They are stimulated by the CSFs which enable them to differentiate and mature.[91]

2.4.3 Types of CSF Medications

Though CSFs are naturally produced in the body, they can also be produced using recombinant DNA technology in laboratories. The 4 distinct types of CSF include: (1) Granulocyte Colony-Stimulating Factor (G-CSF); (2) Macrophage Colony-Stimulating Factor (M-CSF); (3) Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF); and (4) Multipotential Colony-Stimulating Factor (Interleukin (IL) -3]. The FDA licensed G-

CSF and GM-CSF for use in chemotherapy induced neutropenia and marrow damage as they have been demonstrated to be effective for this purpose. Of them, G-CSF is more widely used and has alone, been used to manage 10 – 20 million patients with cancer or neutropenia.[17]

1. G-CSF: G-CSFs stimulate the production of neutrophils, a type of granulocyte. G-CSFs are the most important regulators of neutrophil production levels. They are primarily used for chemotherapy induced and nonmalignant neutropenia. G-CSFs work by reducing the time of transition from stem cell to mature neutrophil, leading to a large amount of functional and mature neutrophils circulating in the body.[89] Some of the brands available include filgastrim (Neupogen) and pegfilgastrim (Neulasta). Filgastrim is the most commonly used G-CSF. The typical dose for Neupogen is 5 mcg/kg daily. The typical dose for Neulasta is 6mg once per treatment cycle. Globally, several biosimilars of filgastrim have been approved with some still in development.
2. GM-CSF: GM-CSFs stimulate the production of two types of white blood cells, both neutrophils and macrophages. The available GM-CSF is sargramostim (Leukine). The dose for Leukine is 250mcg/m^2 daily. [92]
3. M-CSF: M-CSFs stimulate the production of macrophages. Loss of MCS has the greatest effect in reducing monocyte and macrophage population in organs. However, due to a side effect of thrombocytopenia, it has not entered the clinic.

4. Interleukin 3 (IL-3): Loss of IL-3 has a minor effect on the population of granulocytes or macrophages but decreases mast cell levels and some T-cell responses. However, it has not been licensed for use due to side effects.[91]

2.4.4 Clinical Uses

CSFs are used to treat hematological diseases and infections. Most clinical trials that studies CSFs have involved GM-CSF, which are used to treat Human Immuno-deficiency (HIV)-related illnesses, aplastic anemia and cancer. G-CSFs have been used to treat chemotherapy induced and non-malignant neutropenia.

i. HIV-related illnesses: Persons with HIV infections could have abnormal functioning of their white blood cells. The initial clinical trial of GM-CSF was in patients with acquired immunodeficiency syndrome (AIDS) who were neutropenic. The study showed a double increase in their leukocyte counts, with the most significant seen in neutrophils and eosinophils. However, there are concerns that GM-CSF leads to possible HIV replication as seen in some in vitro studies.[93]

ii. Aplastic anemia: CSFs lead to modest neutrophil increases in patients with aplastic anemia. Patients who have severe disease with no evidence of residual myelodysplasia may not respond to GM-CSF.

iii. Myelodysplastic Syndrome: This refers to a group of diseases or disorders that occur due to blood cells that fail to mature or function properly. Trials that have used GM-CSF report an improved neutrophil count and hematologic improvement.[94,95]

iv. Cancer therapy: GM-CSF has been shown to improve neutropenia after chemotherapy in patients with metastatic sarcoma,[96] as well as patients with various solid tumors.[97] Some of the benefits noted include significant decreases in febrile neutropenia, mucositis and need for antibiotic use.[97] Also, both G-CSF and GM-CSF have been used in trials in patients undergoing high-dose chemotherapy with autologous bone marrow transplant for various cancers such as metastatic breast carcinoma, malignant melanoma, Hodgkin lymphoma and non-Hodgkin lymphoma. And across all conditions, neutropenia was reduced, and febrile episodes were fewer.[94,97]

v. Nonmalignant neutropenia: G-CSF have been used in patients with cyclic neutropenia, chronic idiopathic neutropenia and congenital agranulocytosis. In cyclic neutropenia, use of G-CSF has been shown to increase average neutrophil counts.[98] Patients with congenital agranulocytosis have shown continued increases in neutrophil counts and decreased need for antibiotics.[99] Also, G-CSF has been shown to normalize neutrophil counts in patients with chronic idiopathic neutropenia.[100]

vi. Miscellaneous uses: GM-CSF can potentially be used in accidents caused by radiation.[91]

2.4.5 Adverse Effects

Although receiving CSF medications helps reduce hospital admissions and length of stay, they also have some risks and adverse effects. With short acting formulations,

multiple injections are required to deliver the medication. Also, CSFs can cause low-grade fever, headaches, nausea, myalgias and bone pain. Bone pain in the ribs, sternum and back are typically reported with G-CSF and GM-CSF. However, the pain occurs because the bone marrow is making more blood cells.[16,91]

More serious adverse effects have included hypokalemia, hypotension, pulmonary infiltrates, and capillary leak syndrome though most of these effects occurred at higher doses of GM-CSF.[91] Other possible complications include hematological complications such as acute arterial thrombosis, thrombocytopenia, anemia, myeloid leukemia and sickle cell crisis. Some dermatological side effects associated with filgastrim include alopecia, generalized maculopapular rash, reversible acne, and acute febrile neutrophilic dermatosis. Some gastrointestinal effects include diarrhea, mucositis, anorexia, constipation, sore throat and stomatitis.[89]

2.5 Effects of CSF Use in Oncology

CSFs are used in cancer patients undergoing chemotherapy in three different ways: primary prophylaxis, secondary prophylaxis and therapeutic purposes. Primary prophylaxis is usually administered during the first cycle of chemotherapy to prevent the occurrence of neutropenia. Secondary prophylaxis is usually administered after a patient already has neutropenia and it is given to prevent a future occurrence. Therapeutic CSF is administered for treatment purposes. The incidence of neutropenia is highest in the first 2 cycles of first course chemotherapy and is associated with more neutropenic events in later

cycles. Thus, primary prophylaxis of CSF has a synergistic effect in preventing future neutropenic episodes. Furthermore, secondary prophylaxis in subsequent cycles is usually too late to prevent neutropenia.[9]

2.5.1 Primary Prophylaxis

There is substantial evidence on the effect of primary prophylaxis in preventing neutropenia. Several clinical trials over the years have shown the effectiveness and efficacy.[101] The guidelines by ASCO are evidence-based, culling from clinical trials on the effectiveness of CSF for primary prophylaxis.[18] Meta analyses of randomized controlled trials (RCTs) conducted in different patient populations confirmed that primary prophylaxis with CSF reduces the risk of febrile neutropenia during chemotherapy for a solid tumor.[15,102,103] It also reduces the risk of hospitalization and infections.[104,105]

2.5.2 Secondary Prophylaxis

Sometimes a patient who is not at risk for administration of primary prophylaxis suffers neutropenia in a chemotherapy cycle. Secondary prophylaxis could then be administered. However, evidence is lacking on the effectiveness of CSFs in such situations. Mostly, chemotherapy dose reduction or delay is a rational option.[101] But secondary prophylaxis is still supported for patients in which dose reduction could lead to unfavorable outcomes in terms of a disease-free survival or overall survival.[18]

2.5.3 Treatment

The effectiveness of routine use of CSF for therapeutic purposes has not been established as there is limited evidence on its clinical benefits.[106] A 2002 study found no

statistically significant advantage of use of CSF in terms of mortality from FN.[106] Another study found no decrease in overall mortality rates between febrile neutropenia patients treated with antibiotics plus CSF compared patients treated with antibiotics alone.[107] Thus, CSF use for therapeutic reasons is not recommended for patients with afebrile neutropenia by all existing clinical guidelines. However, ASCO recommends that it can only be used in febrile neutropenia when the patient has a high risk of FN or prognostic factors that lead to unfavorable clinical outcomes.[18]

2.6 GUIDELINES FOR CSF USE

Clinical practice guidelines for the utilization of CSFs in patients with neutropenia have been developed by several professional and international oncology organizations, using evidence from RCTs and meta-analysis. Some of the bodies include American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and European Organization for the Research and Treatment of Cancer (EORTC). The initial guideline by ASCO was published in 1994, and was subsequently updated in 1996, 1997, 2000 and 2006, with the most recent being the 2015 update.[108] The NCCN guideline on the use of myeloid growth factors was first published in 2005 with the latest in 2014.[109] The EORTC published guidelines on use of CSF in adults with lymphomas and solid tumors in 2006, with an update in 2010. The EORTC current guidelines were planned to complement the European Society for Medical Oncology (ESMO) guidelines on use of G-CSF for prevention of chemotherapy induced febrile neutropenia in patients with cancer.[88] The focus of this study will be on the ASCO guidelines.

2.6.1 2015 ASCO Guidelines

The ASCO recommendation was a response to problems of costs and adverse events associated with CSF use. The guidelines address the strengths and limitations of CSF use in a wide range of clinical practice settings and were based on a thorough review of evidence.[18]

The recommendations are as follows:

Recommendation 1: Primary prophylactic CSF use starting from the initial chemotherapy and continuing through following cycles is recommended for patients who have a 20 percent or higher risk of febrile neutropenia, based on individual, tumor and treatment related factors. However, effective and safe alternative chemotherapy regimens should be considered.

Recommendation 2: Secondary prophylactic use of CSF is recommended for patients who already had a neutropenic complication from a prior chemotherapy cycle (where primary prophylactic CSF was not given) in which a reduced dose or treatment delay could compromise survival and outcomes. However, reduced dose and treatment delay could be a rational alternative.

Recommendation 3: CSFs should not be regularly administered for cancer patients with neutropenia who are not febrile. Also, CSFs should not be administered regularly as adjunctive treatment with antibiotics in patients with febrile neutropenia. However, CSFs may be used for patients with febrile neutropenia who have an increased risk of infections.

Recommendation 4: Chemotherapy dose-dense regimens with CSF support should only be used in a well-designed clinical trial, or if backed by substantial efficacy data. Though efficacy data supports administering dose-dense chemotherapy in adjuvant treatment of

high-risk breast cancer, there is limited evidence to support its use in non-Hodgkin lymphoma, hence it is not routinely recommended. [Dose-dense regimen refers to a chemotherapy treatment plan in which drugs are administered with less time between treatments than with a standard treatment.]

Recommendation 5: For the purpose of progenitor cell transplantation, CSFs may be administered alone, following chemotherapy, or combined with plerixafor. CSFs should be given after autologous stem cell transplantation to reduce the duration of severe neutropenia. CSFs may be administered after allogeneic stem cell transplantation to reduce the duration of severe neutropenia.

Recommendation 6: CSFs should be not be used in patients receiving concomitant chemotherapy and radiation therapy. If no chemotherapy was given, CSFs may be used therapeutically in patients receiving radiation alone if prolonged delays secondary to neutropenia are expected.

Recommendation 7: [Use in the elderly] Prophylactic CSFs should be considered for patients with diffuse aggressive lymphoma who are 65 years or older treated with curative chemotherapy, especially if the patient has comorbidities.

Recommendation 8: [Use in Pediatric population] The use of CSF in children should be guided by clinical procedures. Like in adults, CSF can be administered as primary or secondary prophylaxis for pediatric patients at high risk of febrile neutropenia. For pediatric situations in which dose intense chemotherapy is known to be beneficial, CSFs should be used to allow the administration of these regimens.

Recommendation 9: Pegfilgastrim, filgastrim, tbo-filgastrim and filgastrim-sndz (and other biosimilars) are recommended for preventing of treatment-related febrile neutropenia. The choice of agent a patient uses depends on cost, convenience or clinical situations.

Recommendation 10: Patients who have been exposed to lethal doses of total-body radiotherapy which are not fatal should be administered CSFs or PEGylated G-CSFs. Factors that are considered risk factors for febrile neutropenia can be found in Table 2.2.

Table 2.2: Patient Risk Factors for Febrile Neutropenia

Risk Factors to Be Considered when estimating Patient's Risk
• Age equal to or above 65 years • Advanced tumor • Previous chemotherapy or radiation therapy • Preexisting neutropenia or bone marrow involvement with tumor infection • Open wounds or recent surgery • Poor performance or nutritional status • Poor renal function • Liver dysfunction, especially elevated bilirubin • Cardiovascular disease • Comorbidity • HIV Infection

Source: Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology.* 2015;33(28):3199-3212.[18]

2.6.2 Consensus & Guidelines Summary

Despite slight differences in the guidelines, all the clinical practice guidelines developed by ASCO, NCCN and EORTC recommend the use of CSF for primary prophylaxis when the risk of febrile neutropenia is 20 percent or more in patients, and secondary prophylaxis if the patient previously had febrile neutropenia in a former cycle and chemotherapy dose reduction or delay will compromise care.[108]

The term ‘primary prophylaxis’ refers to when neutropenia is likely to occur in a patient after chemotherapy, but the patient has no prior experience. The term ‘secondary prophylaxis’ refers to when the patient had neutropenic fever (febrile neutropenia) in the past during a chemotherapy cycle and is expected to have it again. “Supportive uses” of CSF are efforts to reduce the duration of severe neutropenia in patients who are afebrile.

2.7 Issues with CSF Use in Oncology

When CSFs are used appropriately, the risk of toxicities such as febrile neutropenia are reduced in patients. As discussed above, guidelines recommend the routine prophylaxis of CSFs starting from first cycle when the risk of febrile neutropenia is 20 percent or more. The issue with risk assessment is that risk of febrile neutropenia varies with chemotherapy regimens and other factors like disease, treatment and patient specific risk factors. The ASCO guidelines made a distinction between risk factors that increase the chances of neutropenia and risk factors that increase the risk of serious complication or morbidity in patients who develop febrile neutropenia, though some of these factors overlap.

Due to some issues that arise from assessing patient risk of febrile neutropenia, risk models have been developed and used to predict risk of neutropenia in patients receiving chemotherapy. However, model performances have been limited and have challenged its use. These models still require further validation and improvements, which some studies have attempted.[110] An example can be found in Lyman et al. (2011) where a risk model for predicting complications from neutropenia was developed and validated in a population of cancer patients receiving chemotherapy via a prospective cohort study. The authors found

that patient risk of neutropenia was greatest in the first cycle of chemotherapy. The model performance was good, with 90 percent sensitivity, 59 percent specificity, positive predictive value of 34 percent and negative predictive value of 96 percent.[111] A study that assessed the correlation between physician assessed and model predicted risk of febrile neutropenia in patients with non-myeloid tumors receiving found a weak correlation 0.249 (95% C.I, 0.179 – 0.316).[112]

2.8 FACTORS ASSOCIATED WITH CSF USE

Studies have assessed the factors associated with CSF use among cancer patients receiving chemotherapy. Generally, factors found to be associated with clinical use of CSFs include physician, patient, clinical and facility factors. The physician factors include the physician's compensation, knowledge and experience. Patient factors consist of race, comorbidities, geographic factors, patient beliefs and attitudes. Clinical factors include cancer type, disease severity and chemotherapy regimen. The facility factors include practice setting and healthcare setting.[20] For example, a retrospective study assessed the factors associated with primary prophylaxis administration of CSF and variations of CSF administration among older patients with breast cancer using the SEER-Medicare database. The authors showed that significant geographical and racial disparities exist in CSF administration. In particular, a number of SEER regions, for instance California, were more likely to receive prophylactic CSF in comparison to other regions. Also, whites had a higher chance of receiving prophylactic CSF. They equally found that neutropenia risk associated with chemotherapy regimen is predominantly associated with CSF

administration.[9] Another study assessed the use of CSF in a population based cohort of lung and colorectal cancer patients enrolled at Cancer Care Outcomes Research and Surveillance Consortium (CanCORS). The authors found intermediate risk regimen, severe comorbidity and non-HMO enrollment were strongly associated with CSF use. They also found that 96 percent of CSFs were used outside of ASCO and NCCN guidelines.[21]

A retrospective cohort study that analyzed CSF utilization in elderly cancer patients (breast, lung and non-Hodgkin lymphoma) using Medicare data found that chemotherapy cycle and risk associated with chemotherapy regimen are predictors of CSF administration.[22] A study of CSF among breast cancer patients in a clinical practice setting showed that patients who had higher risk regimens were more likely to receive G-CSF primary prophylaxis and achieve relative dose intensity than those with lower risk regimens.[12] In a study of early stage breast cancer patients from a single center, physician perceived risk of febrile neutropenia (FN) in patients largely influenced their decision to use CSF for primary prophylaxis.[113]

2.9 ADHERENCE TO GUIDELINES

CSFs have the potential to be overused and this has remained a problem for decades. Studies have shown that their use is inconsistent with clinical practice guidelines.[21,114-118] This misuse is characterized by both underutilization and overutilization and has been linked to several factors as described above.[20] Studies suggest that the non-adherence to clinical guidelines involves CSFs' underutilization in high risk patients and overutilization in low risk patients.[21,114,115] For instance, a survey of over 1200

ASCO physicians found that 28 percent of respondents used G-CSF prophylactically in patients at low risk for febrile neutropenia (<20%) ,while 48 percent used G-CSF as adjunct to antibiotics to treat febrile neutropenia.[118] Krzemieniecki et al. assessed adherence to guidelines on primary prophylaxis with G-CSF use found that a significant portion (45 – 80%) of all patients across tumor types did not receive the drug in accordance with recommendations. They also found that G-CSF was not administered within the recommended timeframe in patients.[119] Another study assessed the effect of program guidance on prescribing attitudes of G-CSF agents and found a significant increase in use of filgrastim biosimilars and a decrease in use of lenograstim and pegfilgrastim post intervention.[11]

2.10 CANCER CARE INITIATIVES

Due to the high costs associated with cancer care, some initiatives have been launched that are aimed towards improving the quality of care and reducing costs. Some of these initiatives include the Choosing Wisely campaign and the Oncology Care Model (OCM).

2.10.1 Choosing Wisely Campaign

The Choosing Wisely campaign is a 2011 initiative of the American Board of Internal Medicine (ABIM) foundation. The aim of the campaign is to encourage clinician-patient conversations and provide support to patients to choose care that is evidence-based, not repetitive, safe and really needed. Thus, providers and specialists choose wisely by identifying the commonly used tests and procedures in their field of practice whose need

should be questioned. This resulted in a list of recommendations by national organizations that represent medical specialists. The list intends to begin discussions about the relevance of many frequently ordered tests and treatments. The list does not intend to be used as landmark for coverage decisions or exclusions, but to encourage talks about appropriate and necessary treatments.

In addition, the campaign has patient-friendly materials to foster patient empowerment and engagement. There are communication education modules on the Choosing Wisely website [http://www.choosingwisely.org/] to aid providers in developing skills to communicate better with their patients. Furthermore, the ABIM foundation awards grants to support projects and initiatives by organizations that promote the goals of the Choosing Wisely campaign.[120]

2.10.2 Oncology Care Model

The oncology care model was launched by the Center for Medicare & Medicaid Innovation Center. OCM was established in order to develop and test "new payment and service delivery models" that incorporate value and quality in cancer care and promote care that is patient centered. One of the priorities of the OCM is to raise the value of care in oncology. The OCM employs performance-based payment incentives and "practice redesign activities" towards its goal of improving quality while reducing costs. The OCM model was implemented in 2016 and is expected to run until 2021.[121]

2.11 STUDY SIGNIFICANCE

CSFs have been shown to be effective in the management of febrile neutropenia. Though CSFs reduce the incidence and severity of febrile neutropenia, their use for primary prophylaxis comes with significant cost implications which include direct drug acquisition costs and drug administration costs.[113] A 2009 study estimated the cost of filgastrim and pegfilgastrim to be US$270 daily for up to 11 days and US$2100 per dose, respectively.[122] Besides, there are other healthcare costs (direct nonmedical costs and indirect costs) to consider. The costs for the routine use of these medications imposes a financial burden on the health system.[113] The problem of associated costs and adverse events played a role in the development of guidelines for use of CSFs by major cancer societies, including ASCO as detailed above, in order to encourage proper use of medications based on evidence via clinical trials and other factors.[18]

The original clinical guidelines set the clinical threshold for CSF administration at 40 percent risk of febrile neutropenia and the use of CSFs was justified based on economic reasons. But the current threshold puts CSF use at 20 percent risk of febrile neutropenia with the guidelines stating that CSF use should be due to clinical and not financial reasons.[18,90] Due to CSFs being expensive yet important, several studies have carried out cost-effective analyses with varying results. A study that compared primary vs secondary prophylaxis found primary prophylaxis with filgastrim and pegfilgastrim not to be cost effective from the perspective of a publicly funded healthcare system.[123] Besides, studies have shown that pegfilgastrim is the most cost-effective G-CSF, even though filgastrim is more commonly used. Other studies support the cost-effectiveness of pegfilgastrim

compared to filgastrim[122,124] and lenograstim.[124] Moreover, current G-CSF sales are estimated at Canadian $5.2 billion annually,[123] therefore, reducing inappropriate usage of CSF could yield significant cost savings.

The goal of this study was to describe the characteristics of CSF users as well as the prevalence and patterns of CSF use and dose reduction in a population-based cohort of metastatic colorectal cancer patients, to assess the factors associated with CSF use, dose reduction and mortality and to evaluate the compliance to ASCO practice guidelines on use of CSF. This study will help to pinpoint factors associated with inappropriate use of CSF utilization. Targeting these factors could help decrease the inappropriate use of CSFs and may result in enhanced clinical practice, cost savings and improved outcomes.

2.12 Research Questions

The specific research questions this study aims to answer include: In a population of metastatic colorectal cancer patients:

- What are the characteristics of CSF users?
- What is the prevalence of CSF use and dose reduction?
- What are the patterns of CSF administration and dose reduction?
- Is there a significant difference in CSF use pre- vs post-period?
- Is there a significant difference in compliance rates pre- vs post-period?
- What factors predict CSF use?
- What factors predict dose reduction?
- What factors predict all-cause mortality?

- What is the impact of CSF use vs dose reduction on all-cause mortality?

Based on this literature review of past evidence, the general hypothesis is that a combination of patient, clinical, physician and geographical characteristics will influence CSF use in this population. Younger, white, sicker patients with a higher risk of febrile neutropenia and presence of comorbidities are more likely to use CSF than those who do not have these characteristics. Proposed models of the study that addresses these questions and hypotheses can be found in Figures 2.4 to 2.6.

Figure 2.4: Study Model: Predictors of CSF Use, Dose Reduction and Mortality

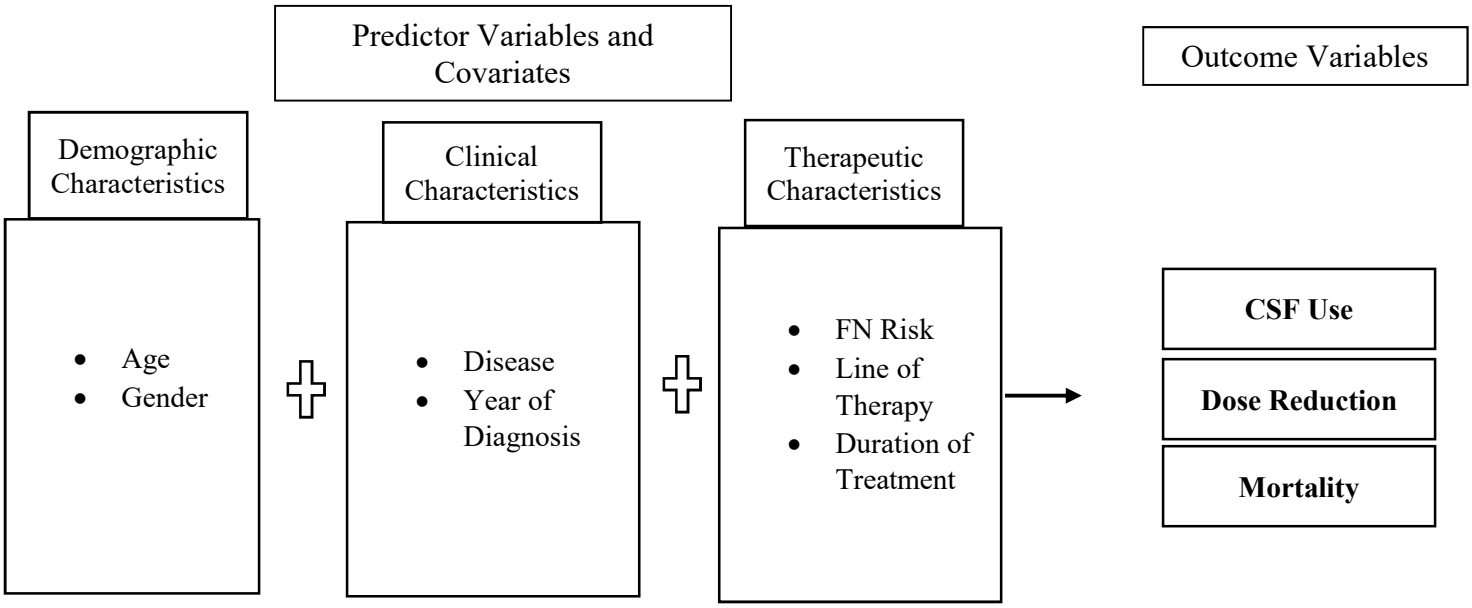


Figure 2.5: Study Model: Comparative Effectiveness of CSF Use vs Dose Reduction on Mortality

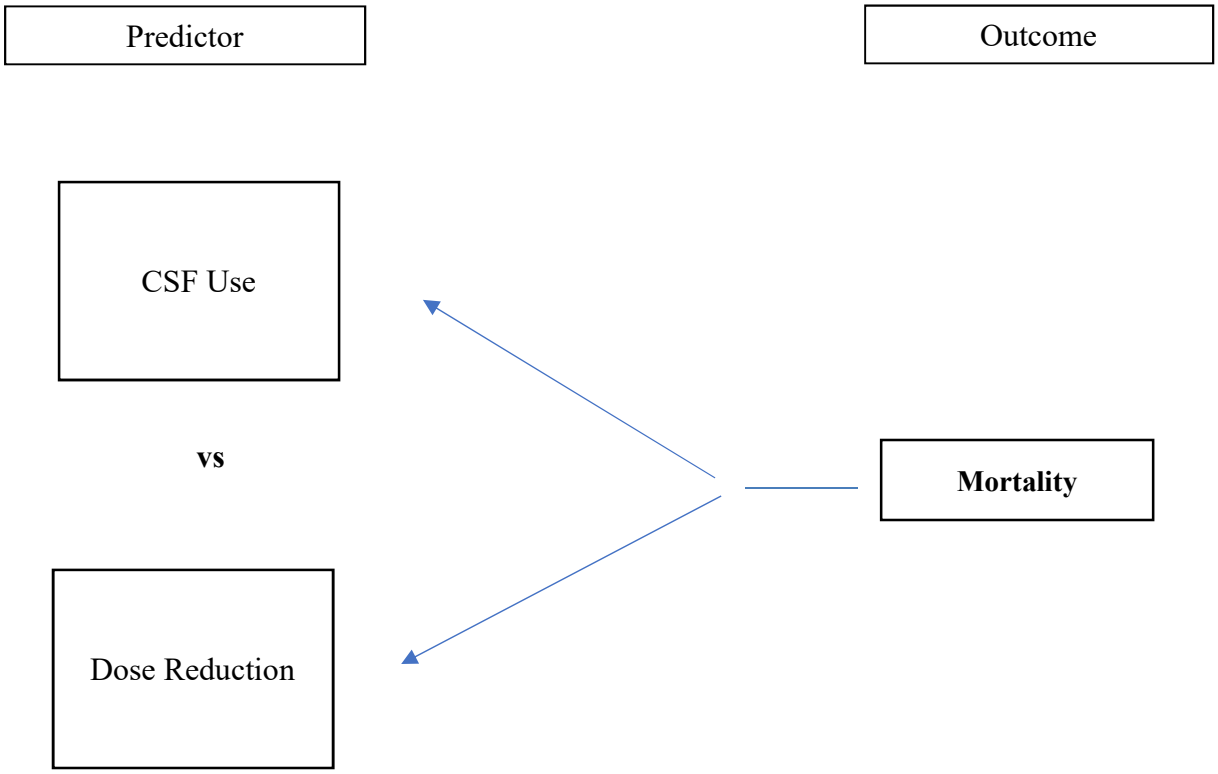
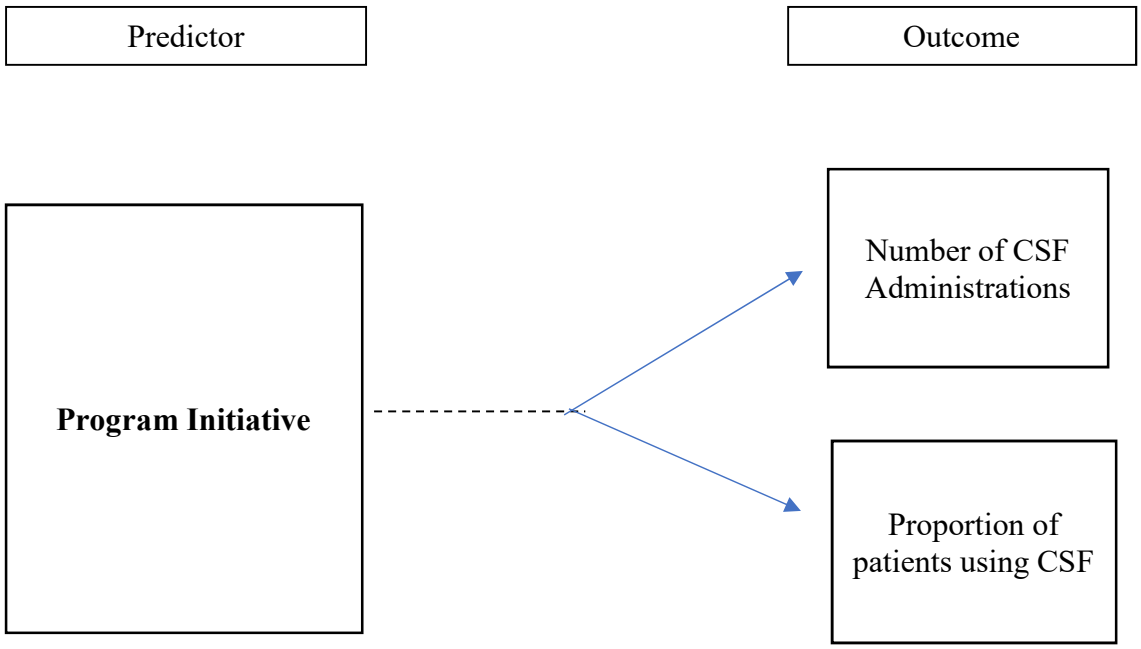


Figure 2.6: Study Model: Impact of Guidelines on CSF Use



CHAPTER 3: METHODOLOGY

This study was designed to describe the use of CSF among metastatic colorectal cancer patients, to examine the impact of a program initiative on use of CSF, to evaluate the compliance of a multi-center oncology practice network to guidelines on CSF use, and to explore the factors associated with CSF use, chemotherapy dose reduction and mortality. This chapter outlines the research methodology that was used to conduct this study. The chapter is divided into nine major sections: study design, study objectives and hypotheses, study variables, the program initiative, data source and sample, ethical procedures, sample size determination, data analysis, and statistical assumptions.

3.1 Study Design

This is a retrospective observational study. All data was obtained from the electronic health records of patients receiving care from a multi-center oncology practice network, which partnered with us to conduct this study. The impact of the program initiative on prescription patterns was evaluated using a pre- vs post- comparison.

3.2 Study Objectives and Hypothesis

The specific objectives and hypothesis of this study were:

Objective 1: To describe the characteristics of CSF users in a cohort of metastatic colorectal cancer patients.

This is to determine the characteristics of all patients in the cohort who received at least one CSF medication during the study period.

Objective 2: To describe the prevalence and patterns of CSF use and chemotherapy dose reduction in a cohort of metastatic colorectal cancer patients.

The frequency of CSF prescriptions was reported for each quarter of the study period. This also assessed the frequency of chemotherapy dose reduction as an alternative to CSF.

Objective 3: To evaluate the impact of a program initiative on CSF use.

This is a comparison of CSF use in the pre- and post-periods.

H1: CSF use will be significantly lower post-initiative compared to the pre-initiative period.

Objective 4: To evaluate the impact of a program initiative on compliance to guidelines.

This objective assessed compliance to ASCO guidelines on CSF use in the pre- and post-periods. .

H2: Compliance to guidelines will be significantly higher post-initiative compared to the pre-initiative period.

Objective 5: To determine the relationship between CSF use (dependent variable) and the variables age, FN risk and year of diagnosis, while controlling for covariates (gender, disease, line of therapy and duration of treatment).

H3a: Age is negatively associated with CSF use after adjusting for covariates. Younger subjects are more likely to receive CSF compared to older subjects**.**

H3b: FN risk is positively associated with CSF use after adjusting for covariates. Subjects with higher FN risk will be more likely to use CSF compared to subjects with lower FN risk.

H3c: Year of diagnosis is positively associated with CSF use after adjusting for covariates. Subjects diagnosed in recent years are more likely to use CSF compared to subjects diagnosed in older years.

Objective 6: To determine the relationship between dose reduction (dependent variable) and the variables age and FN risk. while controlling for covariates (gender, disease, line of therapy, year of diagnosis and duration of treatment).

H4a: Age is positively associated with dose reduction after adjusting for covariates. Older subjects are more likely to receive dose reduction compared to younger subjects.

H4b: FN risk is positively associated with dose reduction after adjusting for covariates. Subjects with higher FN risk will be more likely to receive dose reduction compared to subjects with lower FN risk.

Objective 7: To determine the relationship between all-cause mortality (dependent variable) and the variables age, CSF use and dose reduction, while controlling for covariates (FN risk, gender, disease, line of therapy, year of diagnosis and duration of treatment).

H5a: Age is positively associated with mortality after adjusting for covariates. Older subjects will have higher odds of death compared to younger subjects.

H5b: CSF use is negatively associated with mortality after adjusting for covariates. Subjects who received CSF will have lower odds of death compared to subjects who did not receive CSF.

H5c: Dose reduction is negatively associated with mortality after adjusting for covariates. Subjects who received dose reduction will have lower odds of death than those who did not receive dose reduction.

Objective 8: To compare the effect of dose reduction to the effect of CSF use on all-cause mortality in the population.

H6: The variable 'compare' (CSF Use vs Dose Reduction) is not significantly associated with mortality after adjusting for covariates. There will be no difference in odds of death between subjects who received CSF and subjects who received dose reduction.

3.3 STUDY VARIABLES

The study variables include demographic, clinical and therapeutic characteristics. A description of all variables is detailed below, and their operational definitions can be found in Table 3.1.

3.3.1 Dependent Variables

Primary Dependent Variable

CSF Use: CSF use is defined as the use of the CSF medication pegfilgrastim (Neulasta), during the study time period. The variable was grouped into two categories: 0 for no CSF use, 1 for CSF use.

Secondary Dependent Variables

Dose Reduction: This occurs when a patient's chemotherapy dose is reduced and is defined a10% reduction in chemotherapy dose compared to standard dose at first dosing, or patient

receiving a second dose that is 10% lower than first dose. This had two categories: 1=Dose Reduction 0=No dose reduction

Death (Mortality): Death of patient. This had two categories: 0= No 1=Yes.

3.3.2 Predictor Variables

The predictor variables are grouped into demographic factors, clinical factors, and therapeutic factors.

Demographic variables

Age: patient age at chemotherapy. There was both a continuous and categorical age variable. The categorical age variable was categorized into four groups : <60, 60-70, 70-80, and >80.

Gender: patient gender had two categories : 0 = male, 1 = female.

Clinical variables

Disease: specifies if the patient had colon or rectal cancer and was categorized namely: 0 = rectal cancer, 1 = colon cancer

Year of Diagnosis: refers to the year the patient was diagnosed and was coded into three categories: 0=1988-2007, 1= 2008-2012 and 2=2013-2017.

Therapeutic variables

FN Risk: patient's risk of febrile neutropenia. This was determined from the chemotherapy regimen of the patient. This risk is usually determined by the physician and is associated

with the chemotherapy regimen administered, as well as other disease, treatment or patient specific factors. In order to assign FN risk, the chemotherapy regimen was identified from the data, then patients were grouped into categories based on the risk of the chemotherapy regimen. The categories are: 0 = low risk, 1= intermediate risk. The regimen to risk assessment was based on the NCCN guidelines. The chemotherapy risk categorizations used for this can be found in Table 3.2.

Line of Therapy: refers to the line of treatment the patient received and was categorized as 0 = first line, 1 = second line, 2 = third line and 3 = beyond 3rd line.

Duration of Treatment: refers to the length of time from start to end of chemotherapy and was recoded into three categories: 0= 0-12 months, 1= 13-23 months and 2= 24 and above months.

3.3.3 Other Descriptor Variables

Other descriptor variables include those that were required to calculate and operationally define other variables, and to describe the population.

Chemotherapy regimen: chemotherapy agent administered to the patient. This is a specific drug or drug combination administered and was used to determine the FN risk.

Number of CSF administrations: refers to the number of CSF administrations a patient received. This was used to better describe the population.

Compare: isa variable with two levels created to compare two categories of subjects, 0 = dose reduction and 1= CSF use

Compliance: refers to whether there was compliance to ASCO guidelines on CSF use for each patient and was determined from patient data. ASCO recommends CSF administration for patients with a high risk of FN. CSF use is not recommended for low and intermediate risk patients. A patient was compliant if they received CSF given that they have a high-risk regimen, or if they did not receive CSF and were at low or intermediate risk.

3.4 THE PROGRAM INITIATIVE

The Choosing Wisely campaign was developed and implemented to address the overuse of some tests and treatments in clinical practice with a general aim of avoiding unnecessary or wasteful use of resources. The tests and treatments of concern span across all areas of medical practice such as oncology, cardiology, and emergency medicine, and examples of each include the recommendations against: routine use of breast MRI for breast cancer screening in average risk women, routine electrocardiography screening for asymptomatic patients with myocardial infarction and routine CT scanning of children with mild head injuries, respectively. Choosing Wisely was launched in 2012 by the ABIM Foundation and currently consists of over a million clinicians from over 70 societies as partners.[125]

Beginning March 2016, the multicenter oncology network which partnered with us for this study incorporated a program improvement initiative into their clinical practice with an aim of improving appropriate use of CSFs and compliance to ASCO guideline recommendations. Educational materials were sent to all physicians. The evidence-based

recommendations on CSF use were communicated to physicians and a cost-effective approach was recommended for the physicians. By 2017, prior authorization was required for CSF prescription, and CSF use was tracked via electronic health records.

As detailed earlier, ASCO recommends that (1) CSFs be used as primary prophylaxis starting from first chemotherapy cycle when risk of febrile neutropenia is 20 percent or higher. However, alternative, equally effective, and safe chemotherapy regimens not requiring CSF support should be given when available. (2) CSFs should be used as secondary prophylaxis for patients who already had neutropenia from a prior cycle. However, dose reduction or delay is also a reasonable alternative and (3) CSFs should not be used as adjunctive treatment with antibiotics in patients with febrile neutropenia.

In this study, compliance was defined as a patient receiving CSF if at high risk, or not receiving CSF if not at high risk.

Table 3.1: Study Variables and Operational Definitions

Variable	Operational Definition	Categories
Dependent		
CSF Use	Use of pegfilgrastim (Neulasta) during study time period.	0 = patient did not receive CSF 1 = patient received CSF

Table 3.1: Study Variables and Operational Definitions (Cont'd)		
Secondary Dependent		
Dose Reduction	Up to 10 percent reduction in dose of chemotherapy compared to standard dose	0 = No 1 = Yes
Death (Mortality)	Mortality status of patient	0= No 1= Yes
Independent		
Demographic Factors		
Age	Age at chemotherapy (years)	0= <60 years 1= 60 – 69 years 2= 70 – 79 years 3= 80 and above years
Gender	Patient gender	0= male 1= female
Clinical Factors		
Disease	Colon or rectal cancer	0= rectal cancer 1= colon cancer
Year of Diagnosis	Year patient was diagnosed	0 = 1988- 2007 1= 2008- 2012 2= 2013- 2017
Therapeutic Factors		
FN Risk	Patient's risk of febrile neutropenia (was determined from chemotherapy regimen using NCCN guidelines)	0= Low risk 1= Intermediate risk
Line of Therapy	The line of treatment patient received	0= first line

		1= second line 2= third line 3= beyond the third line
Duration of Treatment		0= 0 – 12 months 1= 13- 23 months 2= 24 and above months
Other descriptor Variables		
These variables are required to calculate and operationally define outcome variables.		
Chemotherapy regimen	Chemotherapy agent or combination of agents administered to the patients. This will be used to assign FN risk.	
No. of CSF Administrations	Number of CSF administrations a patient received	0 = 0 administrations 1= 1-10 administrations 2= 11-20 administrations 3= >20 administrations
Compare	A variable with two levels	0= dose reduction 1= CSF Use
Compliance	Compliance to ASCO recommendations on use of CSF. Compliant: patient received CSF if they have a high-risk regimen, or did not receive CSF if they have a low or intermediate risk regimen Non-compliant: patient received CSF but was at low or intermediate risk	

Table 3.2: Chemotherapy Regimen Risk Categorizations

Agent/Combination of Agents	Regimen Name	FN Risk
Irinotecan, leucovorin, fluorouracil	FOLFIRI	Low
FOLFIRI+ bevacizumab		Low
Fluorouracil	5-FU	Low
Panitumumab	Panit	Low
Irinotecan	IRIN	Low
Bevacizumab	BEVACIZ	Low
Cetuximab	CETUX	Low
Capeox		Low
Oxaliplatin		Low
Fluorouracil, Bevacizumab, Irinotecan, Leucovorin, Capecitabin	5-FU|Bevaciz|Irin|LV|XELO	Low
Fluorouracil, Bevacizumab Leucovorin	5-FU|Bevaciz|LV	Low
Fluorouracil, Irinotecan Leucovorin, Panitumumab	5-FU|Irin|LV|Panit	Low
Fluorouracil, Irinotecan, Ziv-Aflibercept	5-FU|Irin|Ziv-Aflib	Low
Fluorouracil, Leucovorin, Oxaliplatin, Panitumumab	5-FU|LV|Oxali|Panit	Low
Fluorouracil, Bevacizumab	5-FU|Bevaciz	Low
Fluorouracil, Cetuximab, Irinotecan, Leucovorin,	5-FU|Cetux|Irin|LV	Low
Fluorouracil, Leucovorin calcium, Oxaliplatin	FOLFOX	Intermediate
Fluorouracil, Leucovorin calcium, Oxaliplatin, Bevacizumab	FOLFOX + Bev	Intermediate

Table 3.2: Chemotherapy Regimen Risk Categorizations (Cont'd)		
Fluorouracil, Irinotecan hydrochloride, Leucovorin, and Oxaliplatin	FOLFIRINOX	Intermediate
Fluorouracil, Irinotecan, Leucovorin, Oxaliplatin, Bevacizumab	FOLFIRINOX + Bev	Intermediate
Fluorouracil, Leucovorin, Oxaliplatin, Panitumumab	5-FU|LV|Oxali|Panit	Intermediate
Fluorouracil, Bevacizumab, Irinotecan, Oxaliplatin	5-FU|Bevaciz|Irin|Oxali	Intermediate
Cisplatin, Etoposide	CIS|ETOP	Intermediate
Fluorouracil, Bevacizumab, Leucovorin, Oxaliplatin, Capecitabin	5-FU|Bevaciz|LV|Oxali|Xelo	Intermediate

3.5 DATA SOURCE AND SAMPLE

3.5.1 Data Source

The data used for this study were obtained from the electronic health records of colon and rectal cancer patients enrolled in a multi-center oncology practice. This multi-center oncology practice is an individual network of over 400 physicians and oncology specialists. The practice delivers advanced treatment options and high touch care to cancer patients and spans across three states. It was founded in 1986 and has grown to have over 100 offices in Texas, New Mexico and Oklahoma. The database captures data from more than 175 sites of service in its network and contains patient demographics, disease characteristics and all billed services of enrolled patients.

3.5.2 Sample and Eligibility

The sample used for this study was made up of metastatic colorectal cancer patients receiving care at all sites of the oncology practice network. The criteria used in sample selection and eligibility are as follows:

Inclusion Criteria

Diagnosed with colon or rectal cancer

Currently in metastatic stage (i.e., stage 4)

Received chemotherapy

Exclusion Criteria

Colorectal cancer patients in stages 0 to 3

3.6 ETHICAL PROCEDURES

The study was carried out according to the human subjects' research guidelines of The University of Texas Institutional Review Board (IRB). An IRB application was submitted for this study and the protocol was approved. Also, the data were obtained and analyzed in de-identified form to protect patient privacy.

3.7 SAMPLE SIZE DETERMINATION

Power analysis was conducted *a priori* using the G power 3.1.9.2 software. This was necessary in order to determine the minimum sample size required for each analysis in the study. For *a priori* calculation, the required sample size of a study (N) is based on three parameters: the required power level, the prespecified significance level, and the population effect size.[126] Sample size was determined for all possible analyses in this study. It was based on a power of 0.80, an alpha of 0.05 and conventional medium effect sizes. Using a medium effect size of 0.5, the results gave a minimum total sample size requirement of 128 (64 in each group) for a t test analysis. One rule of thumb for logistic regression sample size, is to use 10 – 20 subjects per independent variable,[127] which results in a required sample size of 80 – 120 for this study. The minimum total sample size requirement for a t-test and chi-square analyses (two tailed) using conventional effect sizes[128] can be found in Table 3.3.

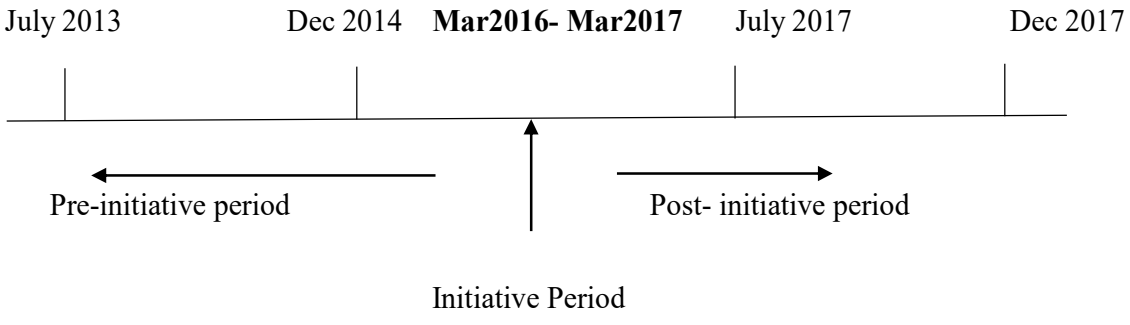
Table 3.3: Power Analysis

Analysis	Power	alpha	Effect size	Sample size
T – test	0.80	0.05	0.50	128
Chi-square goodness of fit	0.80	0.05	0.30	143

3.8 DATA ANALYSIS

All data for this study were analyzed using SAS version 9.4 (SAS Institute, Cary, N.C). The *a priori* base alpha level was set at 0.05. The pre- and post- initiative periods were defined as July 1, 2013 to December 31, 2014 and July 1, 2017 to December 31, 2017, respectively. The program initiative was implemented starting March 2016, up till 2017.

Figure 3.1 Data Extraction and Subject Identification Period



Descriptive Statistics:

Descriptive statistics (means, standard deviations, frequencies and percentages) were performed on all study variables to determine the baseline characteristics of the sample and to determine the prevalence and patterns of CSF use and dose reduction. Means and standard deviations were used to describe the continuous age variable while frequency and percentages were used to describe gender, the categorized age variable, type of disease, year of diagnosis, line of therapy, duration of therapy, FN risk and the categorized number of CSF administrations.

Chi-squared analyses:

Chi squared tests were used to determine the difference in patient characteristics between the pre and post groups and between CSF users and non-users. Chi squared tests were used for categorical variables. Fishers exact test was used for variables whose contingency table cells had expected counts less than 5.

T-test analyses:

T tests were conducted to determine the difference in patient characteristics between the pre and post groups and between CSF users and non-users. T tests were used for continuous variables.

Logistic Regression:

Logistic regression models were used to explore the factors associated with CSF use, factors associated with dose reduction and factors associated with mortality in the population. These models determined the predictive ability of each of the predictor variables, while controlling for covariates. The model is as follows:

Logit [(Y)] = log (π/1-π) = b0 + b1X1 + b2X2 + b3X3 + b4X4 + b5X5 + b6X6 + b7X7 + *e*i, where

π = probability of success (CSF Use = 1)

1 – π = probability of failure (CSF Use = 0)

Y1= CSF Use

Y2= Dose Reduction

Y3= Mortality

b0= intercept

X1= age

X2= FN risk

X3= year of diagnosis

X4= gender

X5= disease

X6= line of therapy

X7= duration of treatment

*e*i= error term

Y is the dependent variable CSF use for the first model, dose reduction for the second model, and mortality for the third model. The Bs are the regression coefficients of the independent variables. The logistic regression analyses were conducted in two steps. First, a univariate model was run independently for the dependent variable and each covariate and results reported in a table as unadjusted analyses. Then, the significant variables at the 5 percent significance level were included for the multivariate models. This was to create more parsimonious final models.

3.9 STATISTICAL ASSUMPTIONS

T-Test Assumptions

The t test assumptions of linearity, normality, independence and homoscedasticity were assessed before running the analyses.[129] To assess the normal assumption, the peakness and symmetry of the distribution were determined using skewness and kurtosis. Scatterplots were used to assess the linearity assumption while residual vs fitted plots were used to assess the constant variance assumption.

Chi-square Assumptions

The chi square assumptions of independence and expected cell count were assessed prior to running the analyses. The assumption of independence means that the data should not be correlated or matched pairs. If the two groups are related, then a different test must be used. The value of the expected cell counts should be five or more and each cell should have a count of one or greater. Also, the data in the cells should be counts, not percentages or transformations of the data.[130] For instances where the assumptions were not met, a fishers exact test was used.

Logistic Regression Assumptions

The assumptions of a logistic regression analysis were likewise assessed before running the analyses. The assumptions include independence of errors, linearity in logit, absence of multicollinearity and absence of strong outliers. The independence of errors assumes that the observations in the data are independent and there are no duplicate responses. This was met by the data in this study, as there are no repeated measures or duplicate outcomes. The linearity in logit assumption assumes a linear relationship between

the continuous independent variables and their log odds (i.e., its logit transformed outcomes).[127]

The assumption of absence of multicollinearity means that the independent variables are not redundant or correlated with each other. A violation of this assumption could lead to large standard errors for the slopes of the variables and can decrease statistical power. This was addressed by eliminating the redundant variables from the model. Multicollinearity in this study was checked by calculating the variance inflation factor (VIF) and spearman correlations of independent variables. Multicollinearity was said to exist when the VIF was greater than 10[131] or tolerance was less than 0.1.

Another assumption is the absence of strong outliers. The presence of strong outliers could compromise the accuracy of the models. Outliers were checked via a visual inspection of residuals in the diagnostic graphs.[127] Logistic regression also requires an adequate sample size. The rule of thumb is to use 10 – 20 events per independent variable, which gives a required minimum sample size of 80 for this study so the large sample size assumption was met.

Table 3.4 contains all the study variables and their measurement levels, while Table 3.5 contains a summary of study objectives, hypotheses and corresponding statistical tests.

Table 3.4: Study Variables and Measurement Levels

Study Variable	Measurement Level
Dependent Variables	
CSF Use	Nominal
Compliance	Nominal
Dose Reduction	Nominal
Independent Variables	
Age	Interval & Nominal
Gender	Nominal
Febrile Neutropenia Risk	Nominal
Disease	Nominal
Year of Diagnosis	Nominal
Line of Therapy	Nominal
Duration of Treatment	Nominal
Other Descriptor Variables	
Chemotherapy Regimen	Nominal
Number of CSF Administrations	Nominal
Compare	Nominal

Table 3.5: Study Objectives, Hypotheses and Corresponding Statistical Tests

<table>
<tr><th>Objectives/Hypotheses</th><th>Dependent Variables</th><th>Independent Variables</th><th>Statistical Tests</th></tr>
<tr><td colspan="4">Objective1: To describe the characteristics of CSF users in a cohort of metastatic colorectal cancer patients</td></tr>
<tr><td colspan="4">Objective2: To describe the prevalence and patterns of CSF use and dose reduction in a cohort of metastatic colorectal cancer patients</td></tr>
<tr><td colspan="4">Objective 3: To evaluate the impact of a program initiative on CSF prescription prevalence</td></tr>
<tr><td>H1: CSF use will be significantly lower post-initiative compared to the pre-initiative period</td><td>CSF Use</td><td></td><td>t-test and Chi-squared test</td></tr>
<tr><td colspan="4">Objective 4: To evaluate the impact of a program initiative on compliance to guidelines</td></tr>
<tr><td>H2: Compliance to guidelines will be significantly higher post-initiative compared to the pre-initiative period.</td><td>CSF Use</td><td></td><td>Chi-sqaured test</td></tr>
<tr><td colspan="4">Objective 5: To determine the relationship between CSF use (dependent variable) and the variables age, FN risk, and year of diagnosis, while controlling for covariates</td></tr>
<tr><td>H3a: There is a significant and negative relationship between age and CSF use while controlling for covariates.</td><td>CSF Use</td><td rowspan="3"><u>Predictors</u>
• Age
• FN Risk
• Year of Diagnosis

<u>Covariates</u>
• Gender
• Disease
• Line of Therapy
• Duration of treatment</td><td rowspan="3">Logistic Regression</td></tr>
<tr><td>H3b: There is a significant and positive relationship between FN risk and CSF use while controlling for covariates.</td><td>CSF Use</td></tr>
<tr><td>H3c: There is a significant and positive relationship between year of diagnosis and CSF use while controlling for covariates.</td><td>CSF Use</td></tr>
<tr><td colspan="4">Objective 6: To determine the relationship between dose reduction (dependent variable) and the variables age and FN Risk while controlling for covariates</td></tr>
</table>

Table 3.5: Study Objectives, Hypotheses and Corresponding Statistical Tests (Cont'd)			
H4a: Age is significantly and positively associated with dose reduction after adjusting for covariates	Dose Reduction	Predictors • Age • FN Risk Covariates • Gender • Disease • Line of Therapy • Duration of treatment	Logistic Regression
H4b: FN risk is significantly and positively associated with dose reduction after adjusting for covariates	Dose Reduction		
Objective 7: To determine the relationship between all-cause mortality (dependent variable) and the variables age, CSF use and dose reduction, while controlling for covariates			
H5a: Age is significantly and positively associated with mortality after adjusting for covariates.	Mortality	Predictors • Age • CSF Use • Dose Reduction Covariates • Gender • Disease • Line of Therapy • Duration of treatment	Logistic Regression
H5b: CSF use is significantly and negatively associated with mortality after adjusting for covariates.	Mortality		
H5c: Dose reduction is significantly and negatively associated with mortality after adjusting for covariates.	Mortality		
Objective 8: To compare the effect of CSF use to the effect of dose reduction on all-cause mortality in the population			
H6: The variable 'compare' (CSF Use vs Dose Reduction) is not significantly associated with mortality after adjusting for covariates.	Mortality	Predictor • A variable 'compare' with two levels: CSF Use and Dose Reduction Covariates	Logistic Regression

		• Gender • Disease • Line of Therapy • Duration of treatment • Age	

CHAPTER 4: RESULTS

The findings of this study are presented in this chapter. The first section describes the data pooling and preliminary analysis. The second section describes the demographics of the study population. The other sections present the statistical analyses, and corresponding results and tables, which are organized by the study objectives. Data were collected at two different time periods (pre-period and post-period). For objectives that involved a pre- vs post- comparison, the entire data set was used. For objectives that did not involve a pre- vs post- comparison, only the pre-period data were used.

4.1 Data Preparation and Cleaning

The data used in this study were obtained from electronic health records of patients in a multi-center oncology practice network. Data were pooled at the regimen level for subjects who met the selection criteria for the two time periods used in this study. The pre-period was defined as 7/1/2013 to 12/31/2014, while the post-period was defined as 7/1/2017 to 12/31/2017. The pre-period had 2541 regimens (observations) corresponding to 2131 unique patients, while the post-period had 885 regimens (observations), corresponding to 837 unique patients. The full data set consisted of a total number of 3426 regimens, corresponding to 2968 unique patients.

4.2 Preliminary Analysis

Data were assessed for normality and missingness. To assess normality, the distribution of all interval level variables had to fall within the threshold of |2| and |7|, respectively. The histograms and Q-Q plots were visually inspected as well [see Appendix

A]. The variables number of CSF administrations and duration of treatment did not meet the normality threshold and were categorized [See Table 4.1]. Although age was normally distributed, it was categorized as well to determine if statistical differences exist based on the different age groups. Missingness was observed in the variables gender (0.03%), duration of treatment (0.03%), FN risk (2.8%) and dose reduction (80.0%). Dose reduction was only available in the pre-period data and had 80% missingness. The observed missingness was not at random but systematic, because the dose reduction variable was only available for patients who had a baseline oncology care model (ocm) episode. Due to this, data imputation technique could not be used. Therefore, all analyses that required the dose reduction variable were conducted using the pre-period cohort, and the missingness limits the study.

Table 4.1: Skewness and Kurtosis of Interval Level Variables

Variable	Skewness	Kurtosis
Age (years)	-0.2503	-0.1531
CSF Administrations	60.7044*	60.1559*
Duration of treatment (months)	2.3285*	7.5996*

*skewed

4.3 Demographic and Clinical Characteristics

The baseline characteristics of the subjects are described in this section. The characteristics were described for the entire study population, as well as for each cohort.

There was a total of 3426 regimens. The average age of the population was 61.8 ±12.0 years (median=62.0, mode=59.0), with a range of 19.0 to 89.0 years. The mean duration of treatment was 6.8 months. A majority of the subjects were male (59.4%), more than 60 years of age (58.2%), had colon cancer (74%) and were diagnosed between 2013 and 2017 (65.3%). For the therapeutic characteristics, most of the subjects had low FN risk (56.3%), were treated within a year (87.1%) and were lost to death (54.2%) at the time data were collected. Chi square and fishers' exact tests showed statistically significant differences between the pre- and post- period groups for the variables' year of diagnosis, duration of treatment, CSF administrations and death.

Table 4.2: Characteristics of Study Participants

Variable	Frequency (%)	Mean (SD)		
Age at chemotherapy		61.79 (11.99)		
Duration of treatment (months)		6.76 (6.95)		
Number of Subjects (n=3426)				
Pre – period	2541			
Post – period	885			
		Study group		P value
		Pre-period (%)	Post-period (%)	
Gender (n=3425)[a]				
Female	1392 (40.6)	1044 (41.1)	348 (39.4)	0.3699
Male	2033 (59.4)	1497 (58.9)	536 (60.6)	
Age group (n=3426)				
<60 years	1443 (41.8)	1040 (40.9)	393 (44.4)	0.1487
60 – 69 years	1063 (31.0)	789 (31.1)	274 (31.0)	
70 – 79 years	701 (20.5)	532 (20.9)	169 (19.1)	
80 and above years	229 (6.7)	180 (7.1)	49 (5.5)	
Year of Diagnosis (n=3426)				
88 – 07	126 (3.7)	116 (4.6)	10 (1.1)	<0.0001*
08 – 12	1061 (31.0)	1006 (39.6)	55 (6.2)	
13 – 17	2239 (65.3)	1419 (55.8)	820 (92.7)	
Disease (n=3426)				
Colon cancer	2543 (74.0)	1862 (73.3)	672 (76.0)	0.1213
Rectal cancer	892 (26.0)	679 (26.7)	213 (24.0)	
Line of therapy (n=3426)				
1st line	2015 (58.8)	1462 (57.5)	553 (62.5)	
2nd line	1023 (29.9)	770 (30.3)	253 (28.6)	

3rd line	307 (9.0)	240 (9.5)	67 (7.6)	0.0113*
Beyond 3rd	81 (2.4)	69 (2.8)	12 (1.4)	
FN Risk (n=3331)[a]				
Low	1876 (56.3)	1405 (56.7)	471 (55.2)	0.43
Intermediate	1455 (43.7)	1072 (43.3)	383 (44.9)	
Duration of Treatment (n =3426)				
0 – 12 months	2985 (87.1)	2150 (84.6)	835 (94.4)	<0.0001*
13 – 23 months	331 (9.7)	281 (11.1)	50 (5.6)	
24+ months	110 (3.2)	110 (4.3)	0 (0.0)	
No. of CSF Administrations (n=3426)				
0 administrations	3039 (88.7)	2197 (86.5)	842 (95.1)	<0.0001*
1 – 10 administrations	296 (8.6)	261 (10.3)	35 (4.0)	
11 – 20 administrations	63 (1.8)	55 (2.2)	8 (0.9)	
>20 administrations	28 (0.9)	28 (1.1)	0 (0.0)	
Death (n=3426)				
Yes	1857 (54.2)	1606 (63.2)	251 (28.4)	<0.0001*
No	1569 (45.8)	935 (36.8)	634 (71.6)	

*significant at 0.05
[a]totals do not equal 3426 due to missing responses

4.4 OBJECTIVE 1: DESCRIPTION OF CSF USERS

The first objective was to describe the demographic, clinical and therapeutic characteristics of CSF users in the population. Here, CSF use was defined as distinct CSF users (subjects who received CSF and did not receive dose reduction). The characteristics for the entire cohort and then for each time period (i.e., pre and post-period) are presented. The results are tabulated by CSF use. [See Tables 4.3 and 4.4].

There were 343 CSF users in the entire cohort. The mean age of subjects who used CSF was 59.6 ±11.0 years. A majority of subjects who received CSF were female (47.5%) and were less than 60 years old (50.4%). Most CSF users had colon disease (70.5%), were diagnosed between 2013 and 2017 (61.5%), had an intermediate FN risk (54.7%), received the first line of chemotherapy (61.5%) and were treated for a year or less (81.3%). Furthermore, 54.2% of CSF users were lost to death. The chi square test results comparing the two groups (CSF users vs non-users) showed a significant difference for the variables gender, age, line of therapy, FN risk and duration of treatment. Compared to non-users, CSF users had a significantly lower age, were significantly more likely to be female and have an intermediate FN risk.

Table 4.3: Characteristics of CSF Users and Non-users

Characteristic[a]	**CSF Use**	**No CSF Use**	**Total**	**P-value**
Age, Mean (SD)	59.6 (11.0)	61.9 (12.1)	61.8 (12.0)	0.0002*
Gender, n (%)				
Female	163 (47.5)	1205 (39.7)	1368 (40.6)	0.0049*
Male	180 (52.5)	1833 (60.3)	2013 (59.4)	
Total[b]	343 (100.0)	3038 (100.0)	3381(100.0)	
Age Group, n (%)				
<60	173 (50.4)	1267 (41.4)	1430 (42.3)	
60 – 69	104 (30.3)	943 (31.0)	1047 (30.9)	0.0025*
70 – 79	51 (14.9)	626 (20.6)	677 (20.0)	
80 and above	15 (4.4)	213 (7.0)	226 (6.7)	
Total	343 (100.0)	3039 (100.0)	3382 (100.0)	
Disease, n (%)				
Colon	242 (70.5)	2260 (74.4)	2502 (74.0)	0.1271
Rectal	101 (29.5)	779 (25.6)	880 (26.0)	
Total	343 (100.0)	3039 (100.0)	3382 (100.0)	
Line of Therapy, n (%)				

Table 4.3: Characteristics of CSF Users and Non-users (Cont'd)				
1st line	211 (61.5)	1772 (58.3)	1983 (58.6)	
2nd line	110 (32.1)	901 (29.7)	1011 (29.9)	0.0087
3rd line	14 (4.1)	293 (9.6)	307 (9.1)	
Beyond 3rd	8 (2.3)	73 (2.4)	81 (2.4)	
Total	343 (100.0)	3039 (100.0)	3382 (100.0)	
FN Risk, n (%)				
Low	149 (45.3)	1707 (57.7)	1856 (56.5)	<0.0001*
Intermediate	180 (54.7)	1251 (42.3)	1431 (43.5)	
Total[b]	329 (100.0)	2958 (100.0)	3287 (100.0)	
Duration of Treatment, n (%)				
0 – 12 months	279 (81.3)	2674 (88.0)	2953 (87.3)	
13 – 23 months	51 (14.9)	273 (9.0)	324 (9.6)	0.0013*
24+ months	13 (3.8)	92 (3.0)	105 (3.1)	
Total	343 (100.0)	3039 (100.0)	3382 (100.0)	
Year of Diagnosis, n (%)				
88 – 07	11 (3.2)	114 (3.8)	125 (3.7)	
08 – 12	121 (35.3)	921 (30.3)	1042 (30.8)	0.1619
13 – 17	211 (61.5)	2004 (65.9)	2215 (65.5)	
Total	343 (100.0)	3039 (100.0)	3382 (100.0)	
Death, n (%)				
Yes	186 (54.2)	1639 (53.9)	1825 (54.0)	0.9172
No	157 (45.8)	1400 (46.1)	1557 (46.0)	
Total	343 (100.0)	3039 (100.0)	3382 (100.0)	

[a]column percentages presented, *significant at 0.05

[b]totals do not equal 3426 due to missing responses

4.4.1 Pre vs Post-period Characteristics and Comparisons

Data for this study was obtained from two different time periods. For comparisons, Table 4.4 shows the characteristics of CSF users for both time periods distinctively. The number of patients who received CSF in the pre-period was higher than the number of

patients who received CSF in the post-period. In the post-period, there was no significant difference between CSF users and non-CSF users for any of the variables.

Table 4.4: Characteristics of CSF Users and Non-users at Pre- and Post- Periods

	Pre-period			Post-Period		
Characteristic[b]	**CSF Use**	**No CSF Use**	**P-value**	**CSF Use**	**No CSF Use**	**P-value**
Age, Mean (SD)	59.9 (11.0)	62.3 (12.07)	0.0004*	57.3 (11.2)	60.9 (12.1)	0.0555
Gender, n (%)						
Female	142 (47.3)	878 (40.0)	0.0149*	21 (48.8)	327 (38.9)	0.1925
Male	158 (52.7)	1319 (60.0)		22 (51.2)	514 (61.1)	
Total[c]	300 (100.0)	2197 (100.0)		43 (100.0)	841 (100.0)	
Age Group, n (%)						
<60	148 (49.3)	889 (40.5)	0.0039*	25 (58.1)	368 (43.7)	0.2821
60 – 69	94 (31.3)	679 (30.9)		10 (23.3)	264 (31.4)	
70 – 79	44 (14.7)	464 (21.1)		7 (16.3)	162 (19.2)	
80 and above	14 (4.7)	165 (7.5)		1 (2.3)	48 (5.7)	
Total	300 (100.0)	2197 (100.0)		43 (100.0)	842 (100.0)	
Disease, n (%)						
Colon	208 (69.3)	1622 (73.8)	0.0989	34 (79.1)	638 (75.8)	0.6217
Rectal	92 (30.7)	575 (26.2)		9 (20.9)	204 (24.3)	
Total	300 (100.0)	2197 (100.0)		43 (100.0)	842 (100.0)	
Line of Therapy, n (%)						
1st line	180 (60.0)	1250 (56.9)	0.0045*	31 (72.1)	522 (62.0)	0.3766[a]
2nd line	101 (33.7)	657 (29.9)		9 (20.9)	244 (29.0)	
3rd line	12 (4.0)	228 (10.4)		2 (4.7)	65 (7.7)	
Beyond 3rd	7 (2.3)	62 (2.8)		1 (2.3)	11 (1.3)	
Total	300 (100.0)	2197 (100.0)		43 (100.0)	842 (100.0)	
FN Risk, n (%)						
Low	131 (45.8)	1254 (58.4)	<0.0001*	18 (41.9)	453 (55.9)	0.0721
Intermediate	155 (54.2)	893 (41.6)		25 (58.1)	358 (44.1)	
Total[c]	286 (100.0)	2147 (100.0)		43 (100.0)	811 (100.0)	

Table 4.4: Characteristics of CSF Users and Non-users at Pre- and Post- Periods (Cont'd)						
Duration of Treatment						
0 – 12 months	239 (79.7)	1879 (85.5)	0.0115*	40 (93.0)	795 (94.4)	0.7294[a]
13 – 23 months	48 (16.0)	226 (10.3)		3 (7.0)	47 (5.6)	
24+ months	13 (4.3)	92 (4.2)		0 (0.0)	0 (0.0)	
	300 (100.0)	2197 (100.0)		43 (100.0)	842 (100.0)	
Year of Diagnosis						
88 – 07	11 (3.7)	104 (4.7)	0.6677	0 (0.0)	10 (1.2)	0.5995[a]
08 – 12	117 (39.0)	870 (39.6)		4 (9.3)	51 (6.0)	
13 – 17	172 (57.3)	1223 (55.7)		39 (90.7)	781 (92.8)	
Total	300 (100.0)	2197 (100.0)		43 (100.0)	842 (100.0)	
Death						
Yes	176 (58.7)	1398 (63.6)	0.0947	10 (23.3)	241 (28.6)	0.4464
No	124 (41.3)	799 (36.4)		33 (76.7)	601 (71.4)	
Total	300 (100.0)	2197 (100.0)		43 (100.0)	842 (100.0)	

[a]fisher's exact test used, *significant at 0.05
[b]column percentages presented
[c]totals do not equal the totals due to missing responses

4.4.2 CSF Use vs Dose Reduction vs Both Characteristics and Comparisons

Since some subjects received both CSF and dose reduction, characteristics were compared between subjects who received only CSF, versus subjects who received only dose reduction, versus subjects who received both CSF and dose reduction. As seen in the table below, 300 (46.7%) subjects received CSF, 298 (46.4%) subjects received dose reduction, while 44 subjects received both CSF and dose reduction (6.9%) in the pre-period. The mean age of subjects who received dose reduction (71.0±8.0) and those who received both (70.3±3.2) was higher than those who received CSF (59.9±11.0). Table 4.5 shows the characteristics of subjects for the three groups.

Table 4.5: Characteristics of CSF Users vs Dose Reduction vs Both in the Pre-Period

Characteristic[a]	CSF Use	Dose Reduction	Both	Total	P-Value
Age, Mean (SD)	59.9 (11.0)	71.0 (8.0)	70.3 (3.2)		<0.0001*
Gender, n (%)					
Female	142 (47.3)	123 (41.3)	24 (54.5)	289 (45.0)	0.1388
Male	158 (52.7)	175 (58.7)	20 (45.5)	353 (55.0)	
Total	300 (100.0)	298 (100.0)	44 (100.0)	642	
Age Group, n (%)					
<60	148 (49.3)	19 (6.4)	3 (6.8)	170 (26.5)	<0.0001*
60 – 69	94 (31.3)	108 (36.2)	16 (36.4)	218 (34.0)	
70 – 79	44 (14.7)	129 (43.3)	24 (54.5)	197 (30.7)	
80 and above	14 (4.7)	42 (14.1)	1 (2.3)	57 (8.8)	
Total	300 (100.0)	298 (100.0)	44 (100.0)	642	
Disease, n (%)					
Colon	208 (69.3)	237 (79.5)	32 (72.7)	477 (74.3)	0.0166*
Rectal	92 (30.7)	61 (20.5)	12 (27.3)	165 (25.7)	
Total	300 (100.0)	298 (100.0)	44 (100.0)	642	
Line of Therapy, n (%)					
1st line	180 (60.0)	212 (71.1)	32 (72.7)	424 (66.0)	0.0092*
2nd line	101 (33.7)	66 (22.2)	12 (27.3)	179 (27.9)	
3rd line	12 (4.0)	18 (6.0)	0 (0.0)	30 (4.7)	
Beyond 3rd	7 (2.3)	2 (0.7)	0 (0.0)	9 (1.4)	
Total	300 (100.0)	298 (100.0)	44 (100.0)	642	
FN Risk, n (%)					
Low	131 (45.8)	138 (46.3)	20 (45.5)	289 (46.0)	0.9895
Intermediate	155 (54.2)	160 (53.7)	24 (54.5)	339 (54.0)	
Total[c]	286 (100.0)	298 (100.0)	44 (100.0)	628	
Duration of Treatment, n (%)					
0 – 12 months	239 (79.7)	232 (77.9)	32 (72.7)	503 (78.3)	0.0946
13 – 23 months	48 (16.0)	38 (12.8)	7 (15.9)	93 (14.5)	
24+ months	13 (4.3)	28 (9.4)	5 (11.4)	46 (7.2)	
Total	300 (100.0)	298 (100.0)	44 (100.0)	642	

Table 4.5: Characteristics of CSF Users vs Dose Reduction vs Both in the Pre-Period (Cont'd)					
Year of Diagnosis, n (%)					
88 – 07	11 (3.7)	17 (5.7)	1 (2.3)	29 (4.5)	0.6975
08 – 12	117 (39.0)	115 (38.6)	19 (43.2)	251 (39.1)	
13 – 17	172 (57.3)	166 (55.7)	24 (54.5)	362 (56.4)	
Total	300 (100.0)	298 (100.0)	44 (100.0)	642	
Death, n (%)					
Yes	176 (58.7)	215 (72.1)	32 (72.7)	423 (65.9)	0.0015*
No	124 (41.3)	83 (27.9)	12 (27.3)	219 (34.1)	
Total	300 (100.0)	298 (100.0)	44 (100.0)	642	

[a]column percentages presented, *significant at 0.05
[c]totals do not equal the totals due to missing responses

4.5 OBJECTIVE 2: PREVALENCE AND PATTERNS OF CSF ADMINISTRATION

The second objective was to determine the prevalence and patterns of CSF use and dose reduction in the population. While the first objective analyzed distinct CSF users, the analyses for this objective include all subjects who received CSF, with or without dose reduction. Results are reported by time periods. However, the study period was further divided into quarters, and the prevalence reported for each quarter. [See Tables 4.6 to 4.9].

4.5.1 Prevalence of CSF Use

A total of 11% (N=387) of the population used CSF. Comparing time periods, the proportion of subjects who received CSF in the pre-period was higher (13.5%) than the proportion that received CSF in the post-period (4.9%) [See Table 4.6]. To better compare the frequencies across equal time periods, the pre-period was divided into three time periods of six months each. Comparing across the four time periods, the post-period quarter had the lowest proportion of CSF users [See Table 4.7].

Table 4.6: Frequency of CSF Use

Variable	Pre-period N (%)	Post-Period N (%)	Total
Subjects who used CSF	344 (13.5)	43 (4.9)	387 (11.3)
Subjects who did not use CSF	2197 (86.5)	842 (94.1)	3039 (88.7)
Total	2541	885	3426

Table 4.7: Frequency of CSF Use by Time Periods

Variable	Pre-period N (%)			Post-period N (%)	Total
	July – Dec 2013	Jan – June 2014	July – Dec 2014	July – Dec 2017	
	Period 1	Period 2	Period 3	Period 4	
Subjects who used CSF	117 (14.2)	121 (13.6)	106 (12.8)	43 (4.9)	387
Subjects who did not use CSF	705 (85.8)	771 (86.4)	721 (87.2)	842 (95.1)	3039
Total	822	892	827	885	3426

4.5.2 Prevalence of CSF Administrations

There was a total of 3095 CSF administrations during the study period, with a mean of 0.90±3.71. The mean number of CSF administrations in the pre-period was higher (1.11±4.2) than that of the post-period (0.31±1.6) [See Table 4.8]. To better compare the frequencies across equal time periods, the pre-period was divided into three time periods of six months each. Comparing across the four time periods, the post-period had the lowest proportion of CSF administrations [See Table 4.9].

Table 4.8: Frequency of CSF Administrations

Variable	Pre-period	Post- Period	Total
Number of CSF administrations	2818	277	3095
Mean (SD) number of CSF Administrations	1.11 (4.2)	0.31 (1.6)	0.90 (3.71)

Table 4.9: Frequency of CSF Administrations by Time Periods

Variable	Pre- period			Post-period	Total
	July – Dec 2013	Jan – June 2014	July – Dec 2014	July – Dec 2017	
	Period 1	Period 2	Period 3	Period 4	
Number of CSF Administrations	907	1162	749	277	3095
Mean (SD) number of CSF Administrations	1.10 (4.1)	1.30 (4.8)	0.91 (3.5)	0.31 (1.6)	

Figure 4.1: CSF Use by Quarter

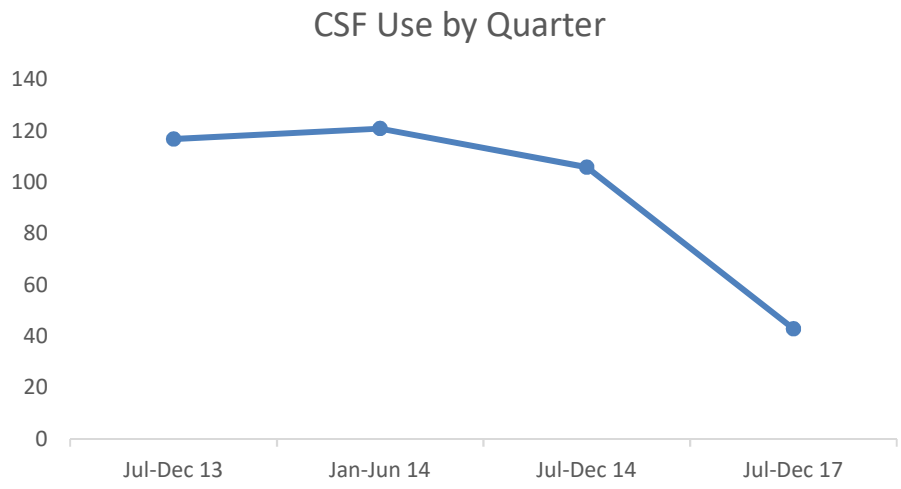
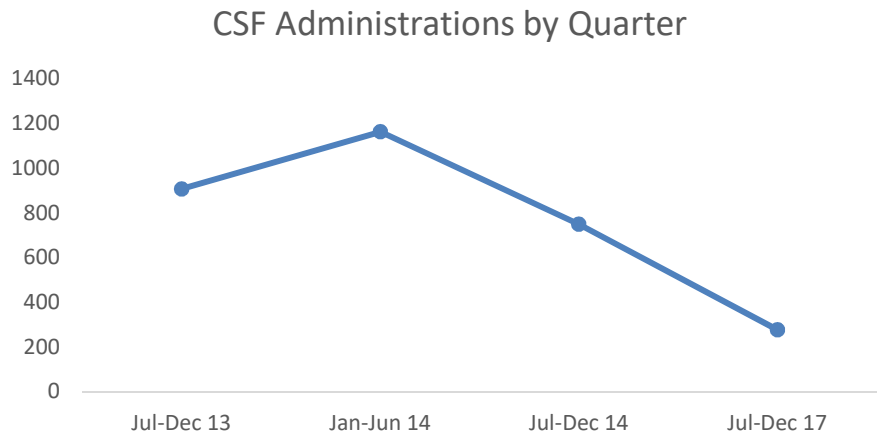


Figure 4.2: CSF Administrations by Quarter



4.5.3 Prevalence of Dose Reduction

The frequency of chemotherapy dose reduction was assessed, and this provided a comparison of patients who received CSF vs those who received dose reduction. However, the dose reduction variable was available for the pre-period data only and had a problem of missingness. So, this was assessed for subjects at baseline who had data on dose reduction.

Of the 508 patients who had data on dose reduction use, 342 (67.32%) received dose reduction, while 166 (32.68%) did not. However, 44 (8.7%) of the patients received both CSF administration and dose reduction.

Table 4.10: Prevalence of CSF Use vs Dose Reduction for the Pre-Period

Variable	CSF Use	No CSF Use	Total
Dose Reduction	44 (8.7)	298 (58.7)	342 (67.32)
No dose Reduction	12 (2.4)	154 (30.3)	166 (32.68)
	56	452	508

4.6 OBJECTIVE 3: IMPACT OF PROGRAM INITIATIVE ON CSF PRESCRIPTION PREVALENCE

The third objective was to evaluate the effect of the program initiative on CSF use. Results are presented in Tables 4.11 and 4.12.

4.6.1 Checking Assumptions

The assumptions of t-test analysis (independence, normality, equal variance) were checked prior to analyses. Although the variable CSF administrations was not normally distributed, the large sample size means that the data distribution should approach a normal distribution. As well, the t-test is fairly robust to the normality assumption so the deviation from normality would not largely impact type 1 error rates.[132] The assumption of equal variance was not met, but this was corrected by using the Satterthwaite p-values instead of the pooled p-values to determine significance. On the contrary, the chi square assumptions of independence and expected cell counts were met.

4.6.2 Analyses Results

H1: CSF use will be significantly lower post-initiative compared to the pre-initiative period.

Results showed a significant difference in means of CSF administrations between the pre- and post-periods ($t=8.05$, $p<0.0001$). The pre-period had significantly higher mean CSF administration (1.11 ± 4.19) than the post-period (0.31 ± 1.60). Also, the maximum number of administrations a patient received in the pre-period was higher than that of the post-period (58 vs 13) [See Table 4.11].

Likewise, there was a significant difference in proportion of patients that used CSF in the pre-period compared to the post-period ($X^2=4.93$, $p<0.0001$). The pre-period had a significantly higher proportion of CSF users (13.5%) than the post-period (4.9%) [See Table 4.12]. Given the results, H1 was supported.

Table 4.11: Impact of Program Initiative on CSF Administrations

	Pre-period (N=2541)	**Post- Period (N=885)**	**T-statistic**	**P-value**
Number of CSF Administrations	2818	277	8.05	<0.0001
Mean (SD) number of CSF administrations	1.11 (4.19)	0.31 (1.60)		
Maximum Administrations a patient received	58	13		

Table 4.12: Impact of Program Initiative on CSF Use

	Pre-period N= 2541	**Post-Period N=885**	**X^2-statistic**	**P value**
Subjects who used CSF, N (%)	344 (13.5)	43 (4.9)	49.35	<0.0001
Subjects who did not use CSF, N (%)	2197 (86.5)	842 (95.1)		

4.7 OBJECTIVE 4: IMPACT OF PROGRAM INITIATIVE ON COMPLIANCE TO ASCO GUIDELINES

The fourth objective was to assess the impact of a program initiative on compliance to ASCO guidelines on CSF use. Only low and intermediate risk regimens were found in the data set; hence patients were deemed compliant if they did not receive CSF.

H2: Compliance will be significantly higher post-initiative compared to the pre-initiative period.

The proportion of patients who did not receive CSF medication in the post-period was higher (95.1%) than the proportion that did not receive in the pre-period (86.5), and this difference was significant ($p<0.0001$). Given the results, H2 was supported. [

Table 4.13: Impact of Program Initiative on Compliance

	Pre-period N= 2541	**Post-Period N=885**	**X^2-statistic**	**P value**
Subjects who used CSF, N (%)	344 (13.5)	43 (4.9)	49.35	<0.0001
Subjects who did not use CSF, N (%)	2197 (86.5)	842 (95.1)		

4.8 OBJECTIVE 5: PREDICTORS OF CSF USE

The fifth objective was to determine the relationships between CSF use (dependent variable) and the variables age, FN risk and year of diagnosis (primary predictors), while

controlling for gender, disease, line of therapy and duration of treatment (covariates). The relationships were assessed using logistic regression models and for the pre-period data.

4.8.1 Checking Assumptions

Each assumption of logistic regression analysis (independence of errors, linearity in logit, absence of multicollinearity and large sample size) was checked prior to analyses. The results showed that none of the assumptions were violated [See Appendix B].

4.8.2 Univariate Logistic Models

Univariate logistic analysis was conducted for each predictor [See Table 4.14]. Variables with significant model p-values were selected for the multivariate analysis. All the variables had model p-values below 0.05 except for year of diagnosis and disease, hence they were removed from the model for the multivariate analysis.

Table 4.14 Logistic Regression Analysis of Factors Associated with CSF Use in the Pre-Period (Unadjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% C.I. of OR	
				Lower Limit	Upper Limit
FN Risk (ref=Low)					
Intermediate	16.11	<0.0001	1.66	1.30	2.13
Age (ref = <60 years)					
60 – 69 years	1.70	0.1921	0.83	0.63	1.10
70 – 79 years	9.67	0.0019	0.57	0.40	0.81
80+ years	5.32	0.0211	0.51	0.29	0.90
Duration of Treatment (ref = 0 - 12 months)					
13 – 23 months	8.77	0.0031	1.67	1.20	2.34
24+ months	0.12	0.7295	1.11	0.61	2.02

Table 4.14 Logistic Regression Analysis of Factors Associated with CSF Use in the Pre-Period (Unadjusted) (Cont'd)					
Line of Therapy (ref= 1st line)					
2nd line	0.24	0.6239	1.07	0.82	1.39
3rd line	10.76	0.0010	0.36	0.20	0.67
Beyond 3	0.36	0.5496	0.78	0.35	1.74
Year of Diagnosis (ref= 88 – 07)					
08 – 12	0.52	0.4698	1.27	0.66	2.44
13 – 17	0.76	0.3844	1.33	0.70	2.53
Gender (ref=Male)					
Female	5.90	0.0151	1.35	1.06	1.72
Disease (ref= Rectal Cancer)					
Colon Cancer	2.72	0.0993	1.25	0.96	1.62

4.8.3 Multivariate Logistic Model

The adjusted logistic model was fit using all covariates that were significant in the univariate analysis at the 5% level. Due to this, all variables except for year of diagnosis and disease were retained for the multivariate analysis. Overall, the logistic regression model was statistically significant at $X^2=63.68$; $p<0.0001$. The results showed a statistically significant relationship between CSF use and the predictors age and FN risk controlling for covariates. A statistically significant relationship was also seen with CSF use and the covariates gender, line of therapy and duration of treatment.

H3a: Age is negatively associated with CSF use after adjusting for covariates. Younger subjects are more likely to receive CSF compared to older subjects.

Age was significantly related to CSF use. The odds of using CSF decreased as age increased. Compared to subjects who were below 60 years, subjects who were in the 70-

79 age group had about 41% decreased odds of using CSF (X^2=8.32; OR=0.59; 95% CI= 0.41, 0.84; p = 0.0039), and subjects who were in the 80+ age group had 56% decreased odds of using CSF (X^2=6.87; OR=0.44; 95% CI= 0.24, 0.81; p= 0.0088). There was no significant difference between subjects who were less than 60 years of age and those in the 60-69 age group (X^2=2.04; OR=0.81; 95% CI= 0.61, 1.08; p = 0.1528). Given the results, H3a was supported.

H3b: FN risk is positively associated with CSF use after adjusting for covariates. Subjects with higher FN risk will be more likely to use CSF compared to subjects with lower FN risk.

The results show that FN risk was significantly related to CSF use. Compared to subjects who had low FN risk, the odds that subjects with an intermediate FN risk received CSF was higher by 83% (X^2=15.24; OR=1.83; 95% CI= 1.35, 2.48; p < 0.0001). Given the results, H3b was supported.

H3c: Year of diagnosis is positively associated with CSF use after adjusting for covariates. Subjects diagnosed in recent years are more likely to use CSF compared to subjects diagnosed in former years.

Year of diagnosis was not significantly related to CSF use. In the univariate analysis, there was no significant difference in CSF use between subjects diagnosed in 1988-2007 and subjects diagnosed in 2008 – 2012 (X^2=0.52; OR=1.27; 95% CI= 0.66, 2.44; p =0.4698) or subjects diagnosed in 2013 – 2017 (X^2=0.76; OR=1.33; 95% CI= 0.70, 2.53; p =0.3844). Given the results, H3c was not supported.

Covariates

Among the covariates, gender, duration of treatment and line of therapy were significantly associated with CSF use. Females had significantly higher odds of using CSF compared to males (X^2=5.88; OR=1.37; 95% CI= 1.06, 1.75; p = 0.0153). Compared to patients whose duration of treatment was 0-12 months, subjects whose duration of treatment was 13-23 months had 60% increased odds of CSF use (X^2=6.67; OR=1.60; 95% CI= 1.12, 2.28; p = 0.0098). There was no significant difference in CSF use between subjects with 0-12 months duration and subjects with 24+ months duration (X^2=0.07; OR=1.08; 95% CI= 0.59, 1.98; p = 0.7934). For line of therapy, subjects who received a 2nd line of therapy had 56% higher odds of using CSF (X^2=7.33; OR=1.56; 95% CI= 1.13, 2.15; p = 0.0068) than subjects who received a 1st line of therapy. Conversely, subjects who received a 3rd line of therapy had 52% lower odds of using CSF (X^2=4.50; OR=0.48; 95% CI= 0.24, 0.95; p = 0.0338) than subjects who received a 1st line of therapy. However, there was no significant difference in CSF use between subjects who received a 1st line of therapy and subjects who had beyond the 3rd line of therapy (X^2=1.77; OR=0.45; 95% CI= 0.14, 1.46; p = 0.1835).

Table 4.15: Logistic Regression Analysis of Factors Associated with CSF Use in the Pre-Period(Adjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
FN Risk (ref=Low)					
Intermediate	15.24	<0.0001*	1.83	1.35	2.48
Age (ref = <60 years)					
60 – 69 years	2.04	0.1528	0.81	0.61	1.08

Table 4.15: Logistic Regression Analysis of Factors Associated with CSF Use in the Pre-Period(Adjusted) (Cont'd)					
70 – 79 years	8.32	0.0039*	0.59	0.41	0.84
80+ years	6.87	0.0088*	0.44	0.24	0.81
Duration of Treatment (ref = 0 - 12 months)					
13 – 23 months	6.67	0.0098*	1.60	1.12	2.28
24+ months	0.07	0.7934	1.08	0.59	1.98
Line of Therapy (ref= 1st line)					
2nd line	7.33	0.0068*	1.56	1.13	2.15
3rd line	4.50	0.0338*	0.48	0.24	0.95
Beyond 3	1.77	0.1835	0.45	0.14	1.46
Gender (ref=Male)					
Female	5.88	0.0153*	1.37	1.06	1.75
Model LR X^2=63.69; DF=10; p< 0.0001					

*significant at p<0.05

4.8.4 Predictors of CSF Use in the Post-Period

For comparison, logistic regression models were also employed to assess the predictors of CSF use in the post-period. The assumptions for multicollinearity were equally tested, and none of the assumptions were violated [see Appendix B]. Univariate analysis was conducted for each predictor. Variables were checked for significance. However, all the variables (age, duration of treatment, line of therapy, year of diagnosis FN risk, gender and disease) had model p-values above 0.05 and hence a multivariate model could not be fit. There was no significant predictor of CSF use in the post-period. [see Table 4.16].

Table 4.16: Logistic Regression Analysis of Factors Associated with CSF Use in the Post-Period (Unadjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
FN Risk (ref=Low)					
Intermediate	3.16	0.0754	1.76	0.94	3.27
Age (ref = <60 years)					
60 – 69 years	2.33	0.1270	0.56	0.26	1.18
70 – 79 years	1.07	0.3015	0.64	0.27	1.50
80+ years	1.31	0.2519	0.31	0.04	2.31
Duration of Treatment (ref = 0 - 12 months)					
13 – 23 months	0.15	0.6995	1.27	0.38	4.25
24+ months	-	-	-	-	-
Line of Therapy (ref= 1st line)					
2nd line	1.52	0.2179	0.62	0.29	1.33
3rd line	0.79	0.3751	0.52	0.12	2.22
Beyond 3	0.16	0.6881	1.53	0.19	12.24
Year of Diagnosis (ref= 88 – 07)					
08 – 12	0.00	0.9742	>999	<0.001	>999
13 – 17	0.00	0.9752	>999	<0.001	>999
Gender (ref=Male)					
Female	1.68	0.1949	1.50	0.81	2.77
Disease (ref= Rectal Cancer)					
Colon Cancer	0.24	0.6223	0.83	0.39	1.76

4.9 OBJECTIVE 6: PREDICTORS OF DOSE REDUCTION

The sixth objective was to determine the relationships between dose reduction (dependent variable) and the variables age and FN risk (primary predictors), while controlling for gender, disease, line of therapy, year of diagnosis and duration of treatment. The relationships were assessed using logistic regression models. Univariate logistic analysis was conducted with each predictor, then the multivariate logistic analysis was conducted with important covariates. The dependent variable dose reduction was dichotomized as 1=yes vs 0=no. The probability modeled was dose reduction=1.

4.9.1 Checking Assumptions

The logistic assumptions (independence, linearity in logit, no multicollinearity and large sample size) that were checked prior to analyses in section 4.8 were valid for the analyses. However, since there was a new dependent variable (dose reduction), the variance inflation factor (VIF) and tolerance were assessed. The results showed that none of the assumptions were not violated [See Appendix B].

4.9.2 Univariate Logistic Models

Univariate logistic analysis was conducted for each predictor [See Table 4.17]. Significant variables were selected for the multivariate analysis. The variables age, diagnosis, gender, line of therapy and disease had model p-values above 0.05 and hence were removed from the model for the multivariate analysis.

Table 4.17: Logistic Regression Analysis of Factors Associated with Dose Reduction (Unadjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
FN Risk (ref=Low)					
Intermediate	12.11	0.0005	1.99	1.35	2.95
Age (ref = <60 years)					
60 – 69 years	0.004	0.9521	1.03	0.46	2.30
70 – 79 years	0.09	0.7619	1.13	0.50	2.52
80+ years	0.10	0.7542	0.87	0.36	2.10
Duration of Treatment (ref = 0 - 12 months)					
13 – 23 months	9.32	0.0023	3.65	1.59	8.38
24+ months	8.88	0.0029	6.28	1.88	21.00
Line of Therapy (ref= 1st line)					
2nd line	0.62	0.4319	0.83	0.53	1.31
3rd line	1.33	0.2495	0.65	0.31	1.36
Beyond 3	3.58	0.0584	0.20	0.04	1.06
Year of Diagnosis (ref= 88 – 07)					
08 – 12	0.00	0.9632	1.02	0.45	2.30
13 – 17	0.43	0.5101	1.31	0.59	2.93
Gender (ref=Male)					
Female	0.68	0.4079	1.18	0.79	1.74
Disease (ref= Rectal Cancer)					
Colon Cancer	1.80	0.1793	0.74	0.47	1.15

4.9.3 Multivariate Logistic Model

The adjusted logistic model was fit using the covariates that were significant in the univariate analysis at the 5% level. Overall, the logistic regression model was statistically significant at $X^2=35.47$; $p<0.0001$. The results showed a statistically significant

relationship between dose reduction and the predictor FN risk. A statistically significant relationship was also seen with dose reduction and the covariate duration of treatment. Results are presented in table 4.18.

H4a: Age is positively associated with dose reduction after adjusting for covariates. Older subjects are more likely to receive dose reduction compared to younger subjects.

Age was not related to dose reduction. The univariate results showed that there was no significant difference in dose reduction between subjects who were less than 60 years of age and those in the 60-69 age group (X^2=0.00; OR=1.03; 95% CI= 0.46, 2.30; p = 0.9521), those in the 70-79 age group (X^2=0.09; OR=1.13; 95% CI= 0.51, 2.52; p = 0.7619), and those in the 80+ age group (X^2=0.09; OR=0.87; 95% CI= 0.36, 2.10; p = 0.7542). Given the results, H4a was not supported.

H4b: FN risk is positively associated with dose reduction after adjusting for covariates. Subjects with higher FN risk will be more likely to receive dose reduction compared to subjects with lower FN risk.

The results show that FN risk was significantly related to dose reduction. Compared to subjects who had low FN risk, subjects with an intermediate FN risk were about two times as likely to receive dose reduction (X^2=11.57; OR=1.99; 95% CI= 1.34, 2.97; p =0.0007). Given the results, H4b was supported.

Covariates

Among the covariates, only duration of treatment was significantly associated with dose reduction. Compared to patients whose duration of treatment was 0-12 months,

subjects whose duration of treatment was 13-23 months were over three times more likely to receive dose reduction (X^2=9.38; OR=3.71; 95% CI= 1.60, 10.24; p = 0.0022). Likewise, subjects whose duration of treatment was 24+ months had even higher odds of receiving dose reduction (X^2=8.61; OR=6.16; 95% CI= 1.83, 20.74; p =0.0034).

Table 4.18: Logistic Regression Results of Factors Associated with Dose Reduction (Adjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
FN Risk (ref=Low)					
Intermediate	11.57	0.0007*	1.99	1.34	2.97
Duration of Treatment (ref = 0 – 12 months)					
13 – 23 months	9.38	0.0022*	3.71	1.60	8.57
24+ months	8.61	0.0034*	6.16	1.83	20.74
Model X2=34.86; DF=3; p< 0.0001					

*significant at p<0.05

4.10 OBJECTIVE 7: FACTORS ASSOCIATED WITH ALL-CAUSE MORTALITY

The seventh objective was to evaluate the effects of covariates on a health outcomes index (all-cause mortality) in the population. This was addressed using the pre-period cohort, due to the longer follow up period that allows for a possible mortality outcome. Logistic regression analyses were used to address this objective. The outcome of interest was all-cause mortality, while the primary predictors of interest were age, CSF use and dose reduction. The covariates included were FN risk, gender, duration of treatment, line

of therapy, disease and year of diagnosis. The dependent variable mortality was dichotomized as 1=yes and 0=no, and the probability modeled was mortality=1. The primary predictor CSF use was dichotomous (1=CSF use vs 0=no CSF use), while dose reduction was dichotomous (1=yes and 0=no).

4.10.1 Checking Assumptions

Again, the logistic regression analysis assumptions (independence of errors, linearity in logit, absence of multicollinearity and absence of strong outliers) were checked prior to analyses. The spearman correlation matrix including all predictors was assessed since all predictors were categorical variables. All results showed no violations in assumptions [See Appendix B].

4.10.2 Univariate Model

Univariate analyses were first run to identify important covariates for the multivariate models. The variables CSF use, disease and year of diagnosis were excluded from the adjusted analysis. Also, dose reduction was run as a separate model in the adjusted analyses due to data missingness. In summary, the main adjusted model was run first, while the second adjusted model was run with dose reduction as a primary predictor. Results of the unadjusted analyses are presented in Table 4.19, while those of the adjusted analysis are presented in Tables 4.20 and 4.21.

Table 4.19 Logistic Regression Results of Factors Associated with All-Cause Mortality (Unadjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
CSF Use (ref= no CSF use)					
CSF Use	2.79	0.0951	0.81	0.63	1.04
FN Risk (ref=Low)					
Intermediate	32.56	<0.0001	0.62	0.53	0.73
Age (ref = <60 years)					
60 – 69 years	6.54	0.0106	1.28	1.06	1.54
70 – 79 years	45.90	<0.0001	2.20	1.75	2.76
80+ years	40.31	<0.0001	3.67	2.46	5.48
Duration of Treatment (ref = 0 - 12 months)					
13 – 23 months	0.40	0.5265	0.920	0.71	1.19
24+ months	28.83	<0.0001	0.34	0.23	0.50
Line of Therapy (ref= 1st line)					
2nd line	56.22	<0.0001	2.05	1.70	2.48
3rd line	38.58	<0.0001	2.76	2.00	3.80
Beyond 3	12.74	0.0004	2.88	1.61	5.15
Gender (ref=Male)					
Female	14.02	0.0002	0.73	0.62	0.86
Disease (ref= Rectal Cancer)					
Colon Cancer	1.28	0.2587	1.11	0.93	1.33
Year of Diagnosis (ref = 88-07)					
08 – 12	2.44	0.1182	0.71	0.47	1.10
13 – 17	4.29	0.0383	0.64	0.42	0.98
Dose Reduction (ref=No)					
Yes	8.59	0.0034	0.48	0.30	0.79

4.10.3 Multivariate Models

Overall, the multivariate logistic regression model was statistically significant at X^2=221.58; p<0.0001. The results showed a statistically significant relationship between mortality and the predictor age. A statistically significant relationship was also seen with mortality and the covariates gender, line of therapy and duration of treatment.

H5a: Age is positively associated with mortality after adjusting for covariates. Older subjects will have higher odds of death compared to younger subjects.

Age showed a significant relationship with mortality. As age of subject increased, the odds of death increased. Compared to subjects who were less than 60 years, subjects in the 60-69 age group had 39% higher odds of death (X^2=10.50; OR=1.39; 95% CI= 1.14, 1.70; p=0.0012). Similarly, subjects in the 70-79 age group were more than twice as likely to die (X^2=53.85; OR=2.44; 95% CI= 1.92, 3.09; p<0.0001), while subjects who were 80 years and above were more than four times as likely to die (X^2=46.04; OR=4.15; 95% CI= 2.75, 6.27; p<0.0001). Given the results, H5a was supported.

H5b: CSF use is negatively associated with mortality after adjusting for covariates. Subjects who received CSF will have lower odds of death compared to subjects who did not receive CSF.

CSF use was not significantly related with mortality. The univariate analysis showed no difference in odds of death between people who used CSF and people who did not (X^2=2.79; OR=0.81; 95% CI= 0.63, 1.04; p=0.0951) [See Table 4.19] hence CSF use was not included in the multivariate analysis. Given the results, H5b was not supported.

H5c: Dose reduction is positively associated with mortality after adjusting for covariates. Subjects who received dose reduction will have lower odds of death than those who did not.

Dose reduction was not significantly related with mortality. There was no difference in odds of death between people who received dose reduction and people who did not (X^2=2.70; OR=0.64; 95% CI= 0.38, 1.09; p=0.1002) [See Table 4.21]. Given the results, H5c was not supported.

Covariates

Among the covariates (based on the main model), duration of treatment, line of therapy and gender showed significant association with mortality. As line of therapy increased, odds of death increased. Compared to subjects who received the 1st line of chemotherapy, subjects who received the 2nd line of therapy had 97 percent higher likelihood of death (X^2=10.50; OR=1.97; 95% CI= 1.58, 2.46; p=0.0012), subjects who received the 3rd line of therapy had even higher odds of death (X^2=53.85; OR=2.67; 95% CI= 1.89, 3.83; p<0.0001), while subjects whose therapy was beyond the 3rd line were more than 4 times more likely to die (X^2=46.04; OR=4.39; 95% CI= 2.18, 8.85; p<0.0001). Compared to subjects who had 0-12 months duration of treatment, subjects who had 24+ months duration of treatment had a 64 percent decreased odds of death (X^2=23.59; OR=0.36; 95% CI= 0.24, 0.54; p<0.0001). There was no statistical difference in odds of death between those who had 0-12 months duration of treatment and those with 13-23 months duration of treatment (X^2=0.03; OR=1.03; 95% CI= 0.78, 1.35; p=0.8521). For

gender, females had significantly lower odds of death compared to males (X^2=12.53; OR=0.73; 95% CI= 0.62, 0.87; p = 0.0004) [See Table 4.20].

Table 4.20: Logistic Regression Results of Factors Associated with All-Cause Mortality (Adjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
FN Risk (ref=Low)					
Intermediate	0.71	0.4005	0.92	0.75	1.12
Age (ref = <60 years)					
60 – 69 years	10.50	0.0012*	1.39	1.14	1.69
70 – 79 years	53.85	<0.0001*	2.44	1.92	3.10
80+ years	46.04	<0.0001*	4.16	2.75	6.27
Duration of Treatment (ref = 0 - 12 months)					
13 – 23 months	0.03	0.8521	1.03	0.78	1.35
24+ months	23.59	<0.0001*	0.41	0.24	0.54
Line of Therapy (ref= 1st line)					
2nd line	36.80	<0.0001*	1.97	1.58	2.46
3rd line	32.41	<0.0001*	2.69	1.89	3.83
Beyond 3	18.50	<0.0001*	4.39	2.18	8.85
Gender (ref=Male)					
Female	12.53	0.0004*	0.73	0.62	0.87
Model LR X^2=221.58; DF=10; p< 0.0001					

*significant at p<0.05

Table 4.21: Logistic Regression Results of Factors Associated with All-Cause Mortality with Dose Reduction as Primary Predictor (Adjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
Dose Reduction (ref= No dose reduction)					
Dose Reduction	2.70	0.1002	0.64	0.38	1.09
FN Risk (ref=Low)					
Intermediate	3.75	0.0529	0.60	0.35	1.00
Age (ref = <60 years)					
60 – 69 years	0.05	0.8272	0.90	0.35	2.31
70 – 79 years	0.72	0.3964	1.50	0.59	3.85
80+ years	2.88	0.0897	2.63	0.86	8.03
Duration of Treatment (ref = 0 - 12 months)					
13 – 23 months	6.51	0.0107*	0.40	0.20	0.89
24+ months	7.48	0.0062	0.32	0.15	0.73
Line of Therapy (ref= 1st line)					
2nd line	4.29	0.0384*	2.12	1.04	4.31
3rd line	0.28	0.6000	1.33	0.46	3.87
Beyond 3	0.54	0.4637	2.28	0.25	20.58
Gender (ref=Male)					
Female	5.89	0.0152*	0.56	0.36	0.89
Model LR X^2=52.64; DF=11; p< 0.0001					

*significant at 0.05

4.11 OBJECTIVE 8: COMPARATIVE EFFECTIVENESS OF CSF USE VS DOSE REDUCTION ON ALL-CAUSE MORTALITY

The eighth objective was to compare the effect of CSF use on all-cause mortality to the effect of dose reduction on all-cause mortality in the population. This was addressed using the pre-period cohort as well, because the pre-period has the dose reduction variable. The variable 'compare' used for this objective, was a categorical variable with two levels; 0=dose reduction and 1=CSF use.

4.11.1 Checking Assumptions

For models with CSF use and dose reduction, the logistic regression assumptions already assessed in objective 7 [see section 4.10] were valid for this analysis. For the new variable compare, the correlation matrix including all predictors including 'compare' was assessed. The results showed that none of the assumptions were violated. [See Appendix B]

4.11.2 Univariate Logistic Models

All univariate analyses for the mortality outcome were conducted in section 4.10 and results displayed in Table 4.19. However, univariate results for CSF use and dose reduction are equally shown in this section for better comparison against the variable 'compare' [See Table 4.22].

4.11.3 Multivariate Logistic Model

The multivariate model comparing the effect of CSF use vs dose reduction on all-cause mortality was significant at X^2=93.08, p<0.0001. The results showed no statistical association between the compare variable and mortality [See Table 4.23].

H6: The variable 'compare' (CSF Use vs Dose Reduction) is not significantly associated with mortality after adjusting for covariates. There will be no difference in odds of death between subjects who received CSF and subjects who received dose reduction.

The variable 'compare' (CSF Use vs Dose Reduction) was not significantly associated with mortality after model adjustment. There was no difference in odds of death between people who received dose reduction and those who received CSF (X^2=1.31; OR=0.78; 95% CI= 0.50, 1.20; p=0.2524). Given the results, H6 was supported. [See Table 4.23].

Table 4.22: Logistic Regression Results of CSF Use, Dose Reduction and 'Compare' on All-Cause Mortality (Unadjusted)

Variable	Wald's X2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
CSF Use (ref= no CSF use)					
CSF Use	2.79	0.0951	0.81	0.63	1.04
Dose Reduction (ref = no dose reduction)					
Dose Reduction	8.59	0.0030	0.48	0.30	0.78
Compare (ref = Dose Reduction)					
CSF Use	11.88	0.0006	0.55	0.39	0.77

Table 4.23: Logistic Regression Results of CSF Use vs Dose Reduction on All-Cause Mortality (Adjusted)

Variable	Wald's X2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
CSF Use (ref= no CSF use)					
CSF Use	0.17	0.6763	0.95	0.73	1.23
Dose Reduction (ref = no dose reduction)					
Dose Reduction	2.70	0.1002	0.64	0.38	1.09
Compare (ref = Dose Reduction)					
CSF Use	1.31	0.2524	0.78	0.50	1.20

Table 4.24: Logistic Regression Results of variable 'Compare' (CSF Use vs Dose Reduction) on All-Cause Mortality (Adjusted)

Variable	Wald's X^2	P-Value	Odds Ratio	95% Confidence Interval of OR	
				Lower Limit	Upper Limit
Compare (ref= Dose reduction)					
CSF Use	1.31	0.2524	0.78	0.50	1.20
FN Risk (ref=Low)					
Intermediate	0.43	0.5137	0.87	0.56	1.34
Age (ref = <60 years)					
60 – 69 years	7.56	0.0060	1.98	1.22	3.21
70 – 79 years	17.50	<0.0001	3.31	1.90	5.81
80+ years	15.86	<0.0001	6.08	2.50	14.77
Duration of Treatment (ref = 0 - 12 months)					
13 – 23 months	0.00	0.9915	1.00	0.59	1.71
24+ months	10.27	0.0014	0.31	0.15	0.64
Line of Therapy (ref= 1st line)					

Table 4.24: Logistic Regression Results of variable 'Compare' (CSF Use vs Dose Reduction) on All-Cause Mortality (Adjusted) (Cont'd)					
2nd line	8.82	0.0030	2.13	1.29	3.50
3rd line	1.35	0.2446	1.80	0.67	4.85
Beyond 3	0.03	0.9867	>999	<0.01	>999
Gender (ref=Male)					
Female	17.65	<0.0001	0.45	0.31	0.65
Model LR X^2=93.08; DF=11; p< 0.0001					

A summary of all objectives, hypotheses tests results, and the corresponding statistical decisions is presented in Table 4.25.

Table 4.25: Results and Statistical Decisions of Hypothesis Tests

Objectives/Hypotheses	Statistical Test	Results	Statistical Decision
Objective1: To describe the characteristics of CSF users in a cohort of metastatic colorectal cancer patients	Descriptive Statistics	N/A	N/A
Objective2: To describe the prevalence and patterns of CSF use and dose reduction in a cohort of metastatic colorectal cancer patients	Descriptive Statistics	N/A	N/A
Objective 3: To evaluate the impact of a program initiative on CSF prescription prevalence			
H1: CSF use will be significantly lower post-initiative compared to the pre-initiative period	t-test and chi-square test	Significant reduction found	Supported
Objective 4: To evaluate the impact of a program initiative on compliance to guidelines			
H2: Compliance to guidelines on CSF use will be significantly higher post-initiative compared to the pre-initiative period	t-test	Significant increase in compliance found	Supported
Objective 5: To determine the relationship between CSF use (dependent variable) and the variables age, FN Risk and Year of Diagnosis, while controlling for covariates			

Table 4.25: Results and Statistical Decisions of Objectives' Hypothesis Tests (Cont'd)			
H3a: Age is negatively associated with CSF use after adjusting for covariates	Logistic Regression	(-) association	Supported
H3b: FN risk is positively associated with CSF use after adjusting for covariates.	Logistic Regression	(+) association	Supported
H3c: Year of Diagnosis is positively associated with CSF use after adjusting for covariates.	Logistic Regression	No association	Not Supported
Significant Covariates: Female gender- (+) association; duration of treatment- (+) association; line of therapy- (+) and (-) association			
Objective 6: To determine the relationship between dose reduction (dependent variable) and the variables age and FN Risk while controlling for covariates			
H4a: Age is positively associated with dose reduction after adjusting for covariates	Logistic Regression	No association	Not supported
H4b: FN risk is positively associated with dose reduction after adjusting for covariates	Logistic Regression	(+) association	Supported
Significant Covariates: Duration of treatment- (+) association			
Objective 7: To determine the relationship between all-cause mortality (dependent variable) and the variables age, CSF use and dose reduction, while controlling for covariates			
H5a: Age is positively associated with mortality after adjusting for covariates.	Logistic Regression	(+) association	Supported
H5b: CSF use is negatively associated with mortality after adjusting for covariates.	Logistic Regression	No association	Not supported
H5c: Dose reduction is negatively associated with mortality after adjusting for covariates.	Logistic Regression	No association	Not supported
Significant Covariates: Line of therapy- (+) association; duration of treatment- (-) association; Female gender- (-) association			
Objective 8: To compare the effect of CSF use to the effect of dose reduction on all-cause mortality in the population.			

H6: CSF Use vs Dose Reduction is not significantly associated with mortality after adjusting for covariates	Logistic Regression	No association	Supported

(+)= positive, (-)=negative

CHAPTER 5: DISCUSSION

This chapter discusses the findings of this study. The opening section gives an overview of the study. The next sections explain the findings as well as related findings from previous research, while the last sections discuss the study limitations and implication and give suggestions for future research.

5.1 STUDY OVERVIEW

This study was aimed at describing the characteristics of patients who used CSF medications in a population of metastatic colorectal cancer patients, and the prevalence and patterns of CSF administration in the population. The study also assessed the impact of a program initiative on CSF use, as well as compliance to guidelines on CSF use. In addition, the study evaluated the factors associated with CSF use, factors associated with dose reduction and factors associated with mortality. The study equally compared the impact of CSF use to dose reduction on a health outcomes index (all-cause mortality). While some studies have assessed CSF utilization and patterns of use among patients with various cancers, there are limited studies that have examined CSF use in metastatic cancer patients. Also, there is scant information in the literature about factors associated with dose reduction and all-cause mortality in such populations. To our knowledge, this is the first study that compares dose reduction to CSF administration and how they impact mortality. This study answers the research questions using data from a multi-center oncology practice network. In comparing this work to the literature, there are some differences that should be noted: i) The G-CSF medication in this study was pegfilgrastim (Neulasta); ii) This study

assessed a metastatic population; and iii) The intent of the CSF administration (whether prophylactic or reactive) was unknown.

5.2 DISCUSSION

5.2.1 Characteristics of CSF Users and Patterns of Use

Overall, CSFs were moderately utilized in this population. The proportion of patients that used CSF distinctively (i.e., without receiving dose reduction) was 10 percent (N=343). Of these, 45 percent of the patients had low FN risk while 55 percent had intermediate FN risk. This was anticipated, as patients with higher risk regimens are more prone to FN, thus more likely to receive growth factors. These findings support extant literature. A population-based cohort study found moderate to high use of CSF (range 9 - 33%) among patients with various cancers, with 9% use amongst the colorectal cancer patients.[21] Another recent study that reviewed the Medicare database to assess use of growth factors in different cancers found most CSF use occurring among higher FN risk patients compared to lower risk patients.[22] However, studies have shown a problem of CSF overutilization in high-risk regimens and underutilization in low-risk regimens.[21,114] No high-risk regimens were identified in the dataset used for this study, which could be due to the patient population being metastatic. Also, in the literature as well as guidelines, CSF administration is not considered as suitable for low and intermediate risk regimens, but CSF use was observed in both low and intermediate risk patients in this study. However, due to lack of data, it was not possible to assess if patients in this study received CSF reactively.. Given that the guidelines support alternatives to CSF administration such as

dose reduction and dose delays, and there is no evidence of the benefit of CSF over dose reduction in metastatic tumors, interventions to reduce CSF use in this population are justified.

5.2.2 Dose Reduction, Compliance to Guidelines and Impact of Guidelines on CSF Use

Cancer consortiums such as ASCO, NCCN and EORTC all recommend using CSF for patients at high risk. No high-risk regimens were identified in the dataset, so compliance for this study meant not receiving CSF. However, ASCO supports use of viable alternatives like dose reduction. In this study, the percentage of patients that received dose reduction in the pre-period was 59 percent, which overall was moderate, even though the dose reduction data was incomplete. A study that estimated the incidence of dose reductions across various types of cancer reported a range of 22.3 – 93.1 percent,[133] although their definition of dose reduction was a 15 percent reduction in chemotherapy dose compared to the standard dose, while in this study dose reduction was operationalized as a 10 percent reduction in chemotherapy dose compared to standard dose. Unfortunately, data were unavailable to assess the prevalence of dose reduction during the post-period and if the program initiative made any impact on physicians' decisions to dose reduce.

Results of this study reveal that educational and regulatory interventions in healthcare settings could have an impact on prescribing behaviors. The pre vs post analysis showed a substantial reduction in CSF use in the post-period compared to the pre-period. The number of patients using CSF as well as the frequency of CSF administrations were both lower in the post-period compared to the pre-period. Also, the proportion of patients

that were deemed compliant in the post-period was significantly higher than that of the pre-period. These findings are similar to a study by Trotta et al. where a pharmaceutical policy educational intervention based on regional guidance on CSF prescription led to a significant decrease in prescription of pegfilgrastim.[11] Another study found that a peer consultation and prescription review intervention reduced inappropriate use of pegfilgrastim, without compromising health outcomes.[134]

5.2.3 Predictors of Dose Reduction

Though guidelines and evidence emphasize the necessity of a full dose intensity for optimal health outcomes, dose reductions and delays are often necessary due to complications like FN. A few studies have assessed factors that influence dose reduction, primary dose reduction, dose delays and/or reduced relative dose intensity. In the literature, primary dose reduction often refers to dose reduction at first chemotherapy cycle,[135] while relative dose intensity (RDI) is defined as the ratio of delivered dose intensity to the standard or planned dose intensity.[136] Though both dose delays and reduced RDI were not assessed in our study, the terms are related, and findings are comparable.

Chemotherapy dose reduction was common in this population (58.7%), when compared to a study of breast cancer patients that found 20 percent of dose reduction and 31 percent of dose delays.[137] The assessment in this study showed that FN risk is a significant predictor of dose reduction, which correlates with findings in previous studies.[137] However, no significant association between age and dose reduction was found, which contrasts with other studies that have found significance with age. Particularly,

studies have found an association between advanced age and a reduced RDI,[133,137] as well as between increasing age and primary dose reduction.[135] This is expected because older patients may be unable to cope with the dose intensity of standard regimens and thus have their doses reduced.[133] The reason for the conflicting findings between the literature and this study could be the missingness of the dose reduction variable.

5.2.4 Predictors of CSF Use

The analyses demonstrate that FN risk, age, gender, line of therapy and duration of treatment are significant predictors of CSF use, with FN risk as the strongest predictor. In line with these findings, a recent retrospective study that assessed CSF use with Medicare data found that most CSF use was for high-risk regimens. The researchers also found greater CSF use in later cycles of therapy, while this study showed higher use in second line of therapy compared to first line, and lower use in third line of therapy compared to first line. Although evidence shows age (being >65) as a critical risk factor in developing FN among cancer patients undergoing myelosuppressive chemotherapy,[111] justifying the need for CSF in older patients, this study found a negative association with age. Likewise, some studies have found that younger patients are more likely to receive CSF,[9,12] which could be due to younger patients receiving more intense regimens which puts them at higher risk of FN compared to older patients. The negative association found with age in this study could be due to physicians deciding on more aggressive treatments which is more tolerable at a younger age. This is important, because aggressive chemotherapy in older and metastatic patients could have a negative effect on patient experiences, and reduce their

quality of life, especially in the last 30 days of life. For this population, it may be more beneficial to dose reduce, which still reduces the risk of FN, and allows for a better quality of life and healthcare experience, for both the patient and family.

For this study, there were no data available on some factors that have been shown to be predictors of CSF use, including physician factors,[20] history of infections, antibiotic administrations and comorbidity.[9,138] Comorbidities are especially important given the age distribution of the population in this study and the metastases state of their tumor. It is very likely that comorbidities would have been important in the physicians' assessment of risk and need for CSF medications.

In the post-period analysis, there was no significant predictor of CSF use and the variations that were significant in the pre-period analysis disappeared. This shows that physicians' prescribing practices changed due to the program initiative.

5.2.5 Predictors of All-Cause Mortality

The overall mortality in the population was high at 54.2 percent, when compared to a study that found 9.5 percent though that was for in-patient mortality. In addition to age, gender, line of therapy and duration of treatment were associated with mortality. The use of CSF in this population did not influence mortality. This correlates with the findings of a meta-analysis of RCTs by Clark et al. that found no influence of CSF use on overall mortality among cancer patients, but did find marginal significance for infection related mortality.[139] Conversely, some studies have found that CSF administration led to a

significant reduction in overall mortality,[140] infection related mortality and early mortality.[15]

Other studies have found factors such as comorbidities, infections and infection-related complications to be associated with mortality.[69,141]

5.2.6 Comparative Effectiveness of CSF Use vs Dose Reduction on All-Cause Mortality

The effectiveness of CSF in reducing FN events and leading to better health outcomes when used for prophylaxis is well documented. Dose reduction has also been shown to play a role in reducing myelosuppression. In comparing dose reduction to CSF use and their effect on mortality, this study found no difference in odds of death between CSF users and patients who received dose reduction. This is important because if there is no difference in the clinical outcomes of both risk reduction strategies, then the cost-effective approach, which is dose reduction, should be used for this population. Studies that compare CSF use to dose reduction in terms of health outcomes are lacking. This finding fills a gap in the literature and yet address a key issue that is important to payers and providers and essential to patient care.

5.3 IMPLICATIONS

There are some economic and clinical implications of this study. For the oncology network whose data were used for this study, expenditure on CSFs have been a concern for years, especially in the pre-period. In 2015, pegfilgrastim was the highest individual drug in billed claims in the network, even though evidence of its benefit for metastatic solid tumors is lacking. From the results of this study, one can estimate significant savings to

payers and buyers. If the significant reduction in CSF use observed in the post-period is sustained over time, and prescribers incorporate the new evidence and adopt the dose reduction approach for this population, increase in savings could be recorded, while maintaining optimal health outcomes.

5.4 Future Directions

There are opportunities for future research identified in this study. To better assess the impact of program initiatives on prescription patterns, a time series analysis could be employed to evaluate the longitudinal effects of the initiative and study the trends at different time points. Due to data constraints, there are several variables of interest (e.g., comorbidities, infections) not explored in this study, which future researchers may include and assess. Also, although we found no difference in mortality between patients who received CSF and those who received dose reduction, mortality alone does not capture the totality of clinical outcomes. Other health outcomes indices that may be of interest to future researchers include number of hospitalizations, length of stay, urgent visits, ED visits, patient satisfaction and health-related quality of life. Future studies are also needed to assess and compare the occurrence of FN and infections in the two groups (CSF users vs patients who received dose reduction).

5.5 Study Limitations

There are several shortcomings in this study which have been categorized into data and methodological limitations.

Data Limitations

Firstly, the data used in this study were obtained from the electronic health records of patients, so there is the possibility of coding inaccuracies especially with data like CSF use and chemotherapy dates. Secondly, the dose reduction variable was obtained via review and calculations of dosing data on patient charts, which is unstructured and may also have problems of inaccuracy. Thirdly, the data do not detail other disease-specific or patient-specific factors or treatment intent that were probably considered by the physician prior to regimen choice. For instance, studies have shown that the presence of chronic comorbidities increases a patient's risk of FN.[138] So it is likely that physicians considered comorbidities in their risk assessment prior to CSF administration, though the data are not available. Moreover, CSF can be used both prophylactically or therapeutically, and prophylactic use can be either primary or secondary. However, the intent of use was not captured in the data, making it difficult to distinguish if CSF use was prophylactic or therapeutic. Finally, the occurrence of febrile neutropenia or other neutropenic events was also not contained in the data.

Methodological Limitations

Commonly, it is recommended that the risk of FN be evaluated by the physician before the first chemotherapy cycle. This risk assessment is often based on patient-, disease- and treatment-related factors, in addition to chemotherapy regimen. Then, the patient is assigned either to a high , intermediate or low risk group. However, there is no general consensus on risk assessment. While both ASCO and NCCN have their criteria to aid in the assessment, physicians may also exercise clinical judgment for individual

cases.[142] FN risk in this study was based on chemotherapy regimen found in the data, which could be a misrepresentation. Also, a few of the chemotherapy regimens found in the data are not included in the examples provided by NCCN and thus were classified as missing values.

In this study, some patients received both CSF and dose reduction, but it was not indicated which was given before the other. Use of CSF may have been due to specific instances of febrile neutropenia and at the physician's discretion, but data were not available for occurrence of febrile neutropenia.

Furthermore, the post-period in this study had a short follow-up (6 months) and it may be too early to tell if the noted change in prescription patterns would remain stable over time.

5.6 CONCLUSIONS

This study investigated and compared the use of CSF and chemotherapy dose reduction among metastatic colorectal cancer patients and factors that influence their use. The results provide estimates of CSF use and patterns of use among the patients, within two time periods. Results demonstrate that CSF use was significantly lower in the post-period, compared to the pre-period. This means that a program initiative that involves education of oncologists, as well as monitoring of CSF prescriptions could significantly alter and positively impact prescription patterns. This approach should be adopted by oncology practices as this could reduce CSF overutilization and improve cost savings.

The multivariate models presented also show the risk factors that predict CSF use as well as dose reduction. FN risk was the most significant predictor of both CSF use and dose reduction. This means that a patient's risk of FN had the greatest influence on a physician's decision to administer CSF or to dose reduce. The study also investigated risk factors that predict mortality in this population, which revealed age and line of therapy as the most significant predictors. While this is vital information, survival analysis involving Kaplan-Meier methods and cox proportional models could be used to better understand the relationships between these predictors and risk of death.

Furthermore, the results showed no difference in odds of death between CSF users and patients who received dose reduction. This indicates no benefit of CSF use over dose reduction in terms of mortality outcome. This is an important finding, given that it is more cost effective to dose reduce than to administer CSF. Also, this is a time where the approach of health delivery is aimed towards reducing costs while improving quality of care, employing services that are patient centered and beneficial. Therefore, this evidence, if incorporated into clinical practice, could help decrease the inappropriate use of CSFs and may result in enhanced clinical practice and cost savings, without negatively impacting health outcomes. However, use of dose reduction alone in this population should be monitored over time to assess its impact on other health outcomes indices, and this should be the focus of future studies.

Appendices

Appendix A: Histograms and QQ plots of Continuous Variables

Figure A1: Distribution of Continuous Variable Age

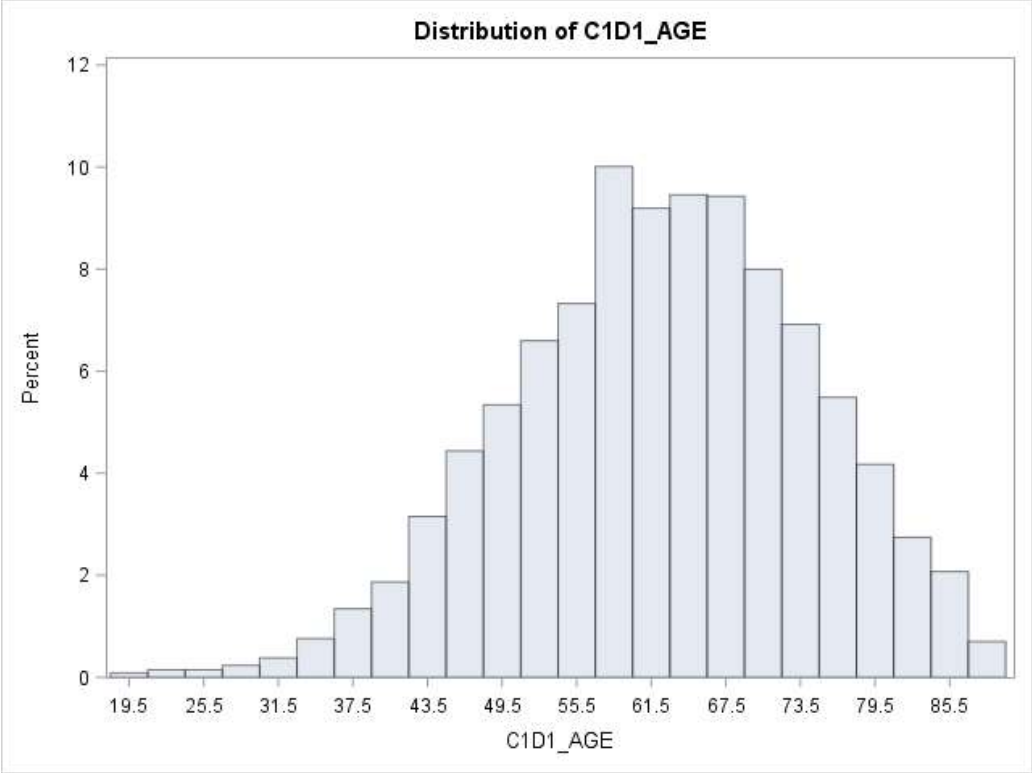


Figure A2: Distribution of Continuous Variable Age showing Normal & Kernel Lines

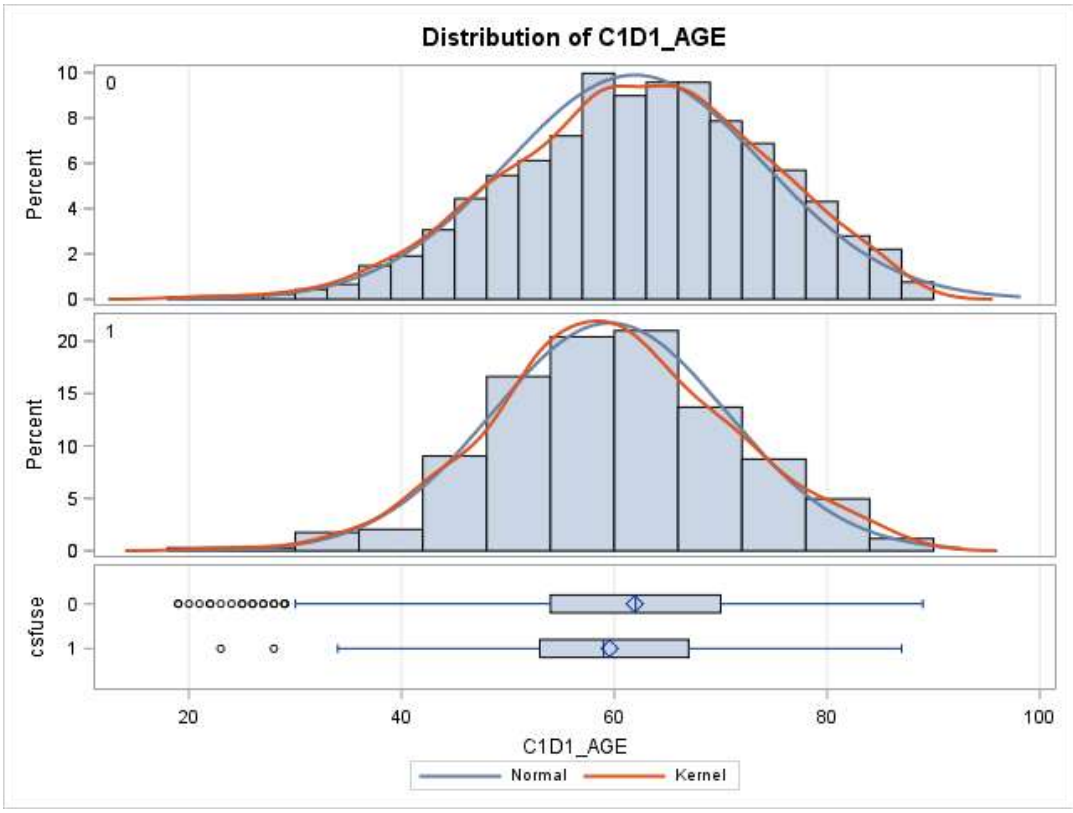


Figure A3: Q-Q Plot of Continuous Variable Age

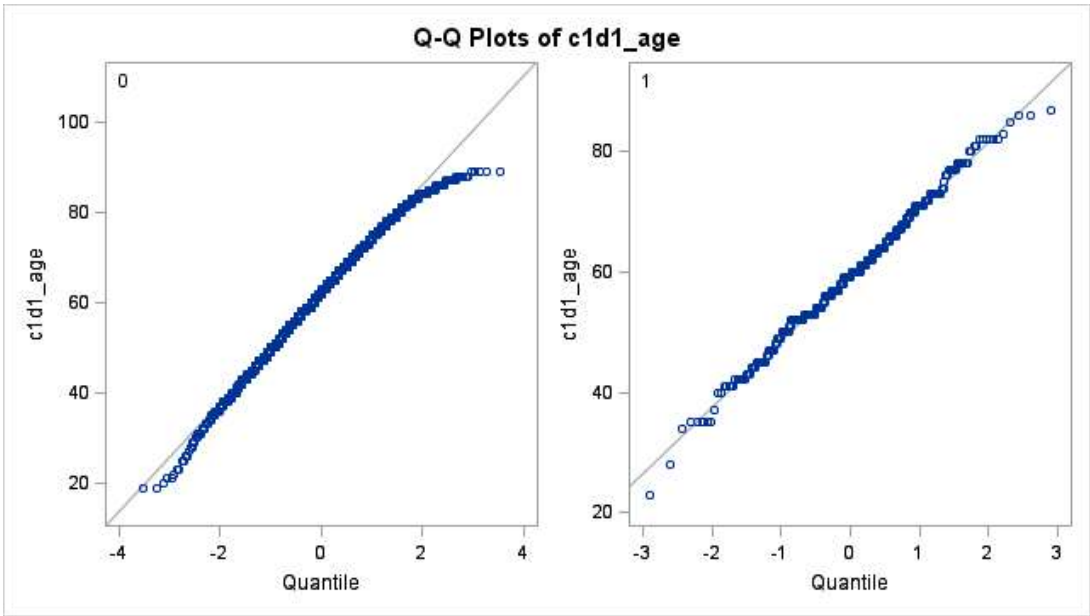


Figure A4: Distribution of Continuous Variable CSF Administration

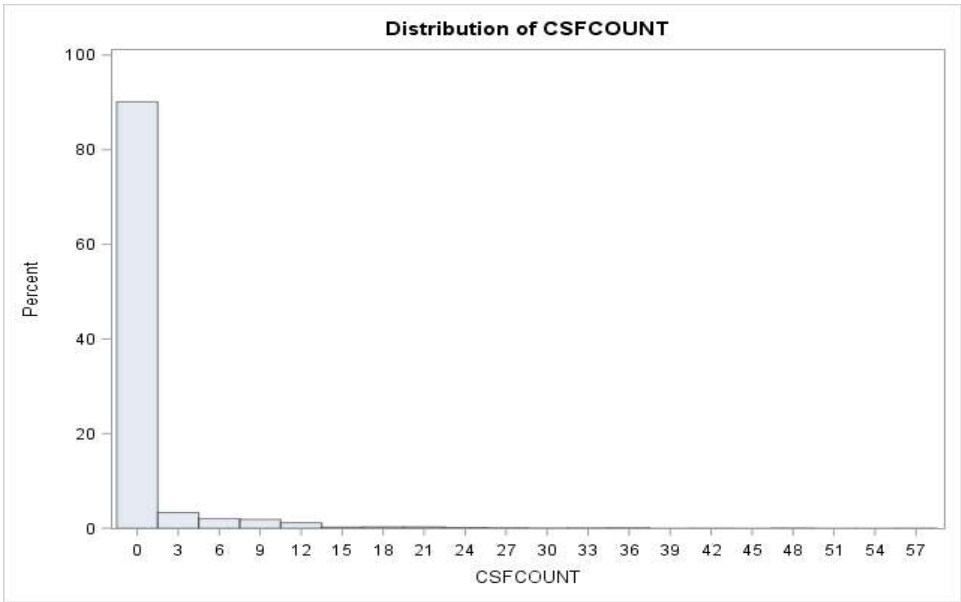


Figure A5: Distribution of Continuous Variable CSF Administration showing Normal & Kernel Lines

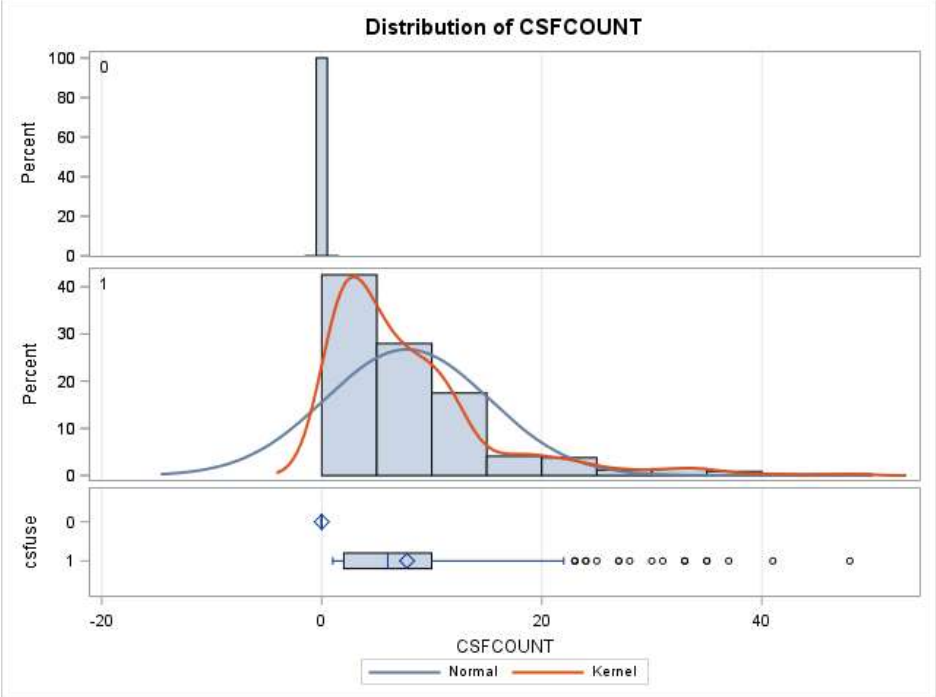


Figure A6: Q-Q Plot of Continuous Variable CSF Administration

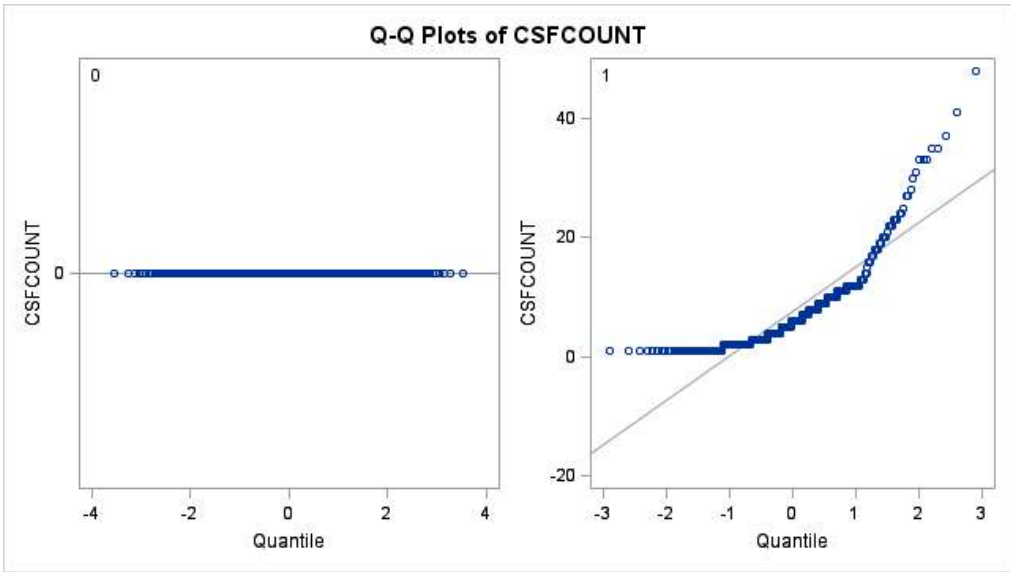


Figure A7: Distribution of Continuous Variable Duration of Treatment

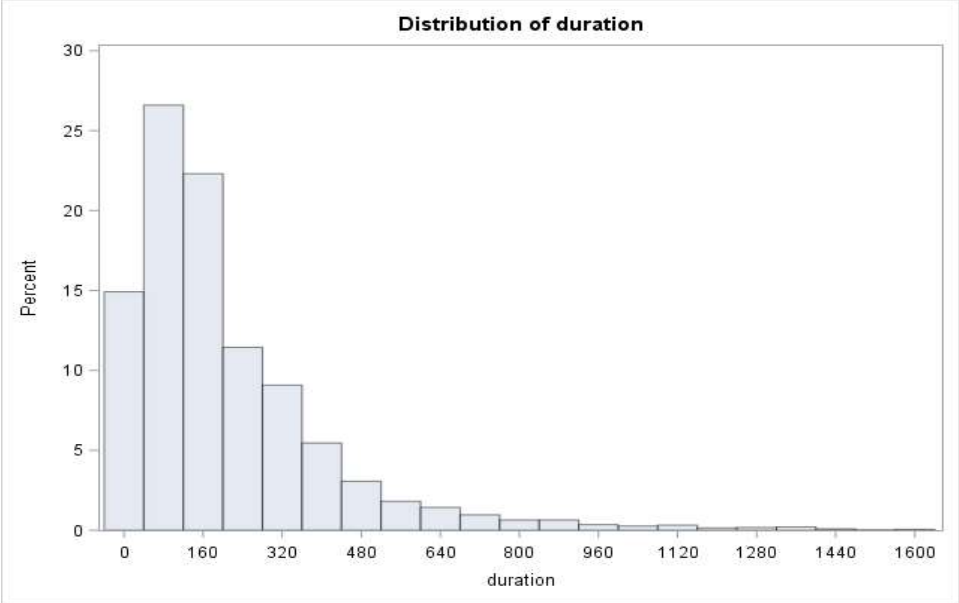


Figure A8: Distribution of Continuous Variable Duration of Treatment showing Normal & Kernel Lines

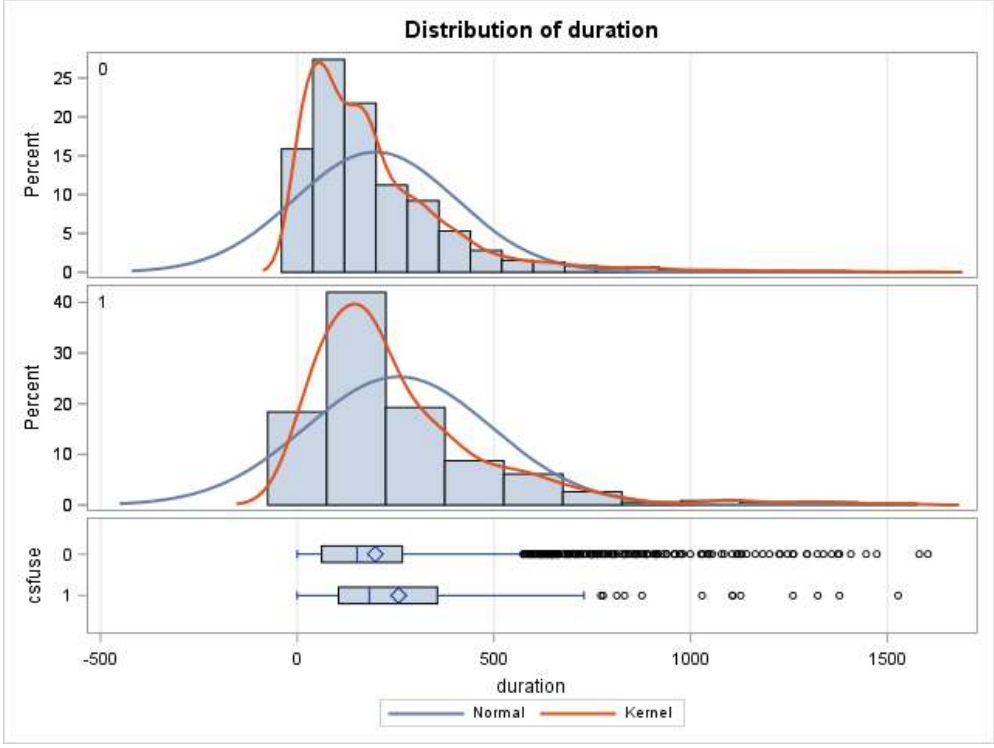
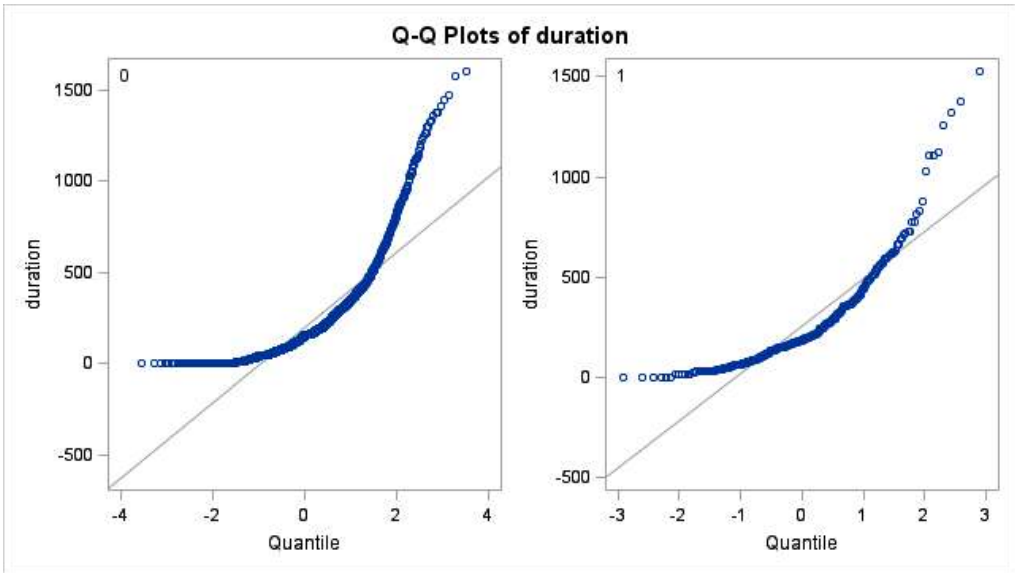


Figure A9: Q-Q Plot of Continuous Variable Duration of Treatment



Appendix B: Multicollinearity Assumption Tests

Figure B1: Spearman correlation for Logistic Regression Model of CSF Use and Covariates in the Pre-Period

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	FNrisk	agecat	sex	duracat	diagnosis	LOT	dxcat
FNrisk	1.00000	-0.02208	0.02771	0.00614	0.32993	-0.51091	-0.06029
		0.2720	0.1679	0.7601	<.0001	<.0001	0.0027
	2477	2477	2477	2477	2477	2477	2477
agecat	-0.02208	1.00000	0.02879	-0.01811	-0.01448	-0.03297	0.08348
	0.2720		0.1468	0.3615	0.4656	0.0966	<.0001
	2477	2541	2541	2541	2541	2541	2541
sex	0.02771	0.02879	1.00000	0.03335	0.03572	-0.01848	0.11565
	0.1679	0.1468		0.0928	0.0718	0.3518	<.0001
	2477	2541	2541	2541	2541	2541	2541
duracat	0.00614	-0.01811	0.03335	1.00000	-0.04510	-0.09047	-0.02450
	0.7601	0.3615	0.0928		0.0230	<.0001	0.2170
	2477	2541	2541	2541	2541	2541	2541
diagnosis	0.32993	-0.01448	0.03572	-0.04510	1.00000	-0.40375	0.02346
	<.0001	0.4656	0.0718	0.0230		<.0001	0.2372
	2477	2541	2541	2541	2541	2541	2541
LOT	-0.51091	-0.03297	-0.01848	-0.09047	-0.40375	1.00000	0.05828
	<.0001	0.0966	0.3518	<.0001	<.0001		0.0033
	2477	2541	2541	2541	2541	2541	2541
dxcat	-0.06029	0.08348	0.11565	-0.02450	0.02346	0.05828	1.00000

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

FNrisk	agecat	sex	duracat	diagnosis	LOT	dxcat
0.0027	<.0001	<.0001	0.2170	0.2372	0.0033	
2477	2541	2541	2541	2541	2541	2541

Figure B2: VIF and Tolerance for Logistic Regression Model of CSF Use and Covariates in the Pre-Period

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Tolerance	Variance Inflation
Intercept	**1**	0.13501	0.02664	5.07	<.0001	.	0
FNrisk	**1**	0.04429	0.01483	2.99	0.0029	0.77949	1.28289
agecat	**1**	-0.02490	0.00688	-3.62	0.0003	0.98705	1.01312
sex	**1**	0.03430	0.01332	2.58	0.0101	0.98234	1.01798
duracat	**1**	0.02038	0.01328	1.53	0.1250	0.98002	1.02039
diagnosis	**1**	-0.00794	0.01248	-0.64	0.5249	0.79940	1.25094
LOT	**1**	-0.01280	0.01016	-1.26	0.2079	0.70397	1.42051
dxcat	**1**	-0.01611	0.01489	-1.08	0.2794	0.97300	1.02775

Figure B3: Spearman correlation for Logistic Regression Model of CSF Use and Covariates in the Post-Period

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	FNrisk	agecat	sex	duracat	diagnosis	LOT	dxcat
FNrisk	1.00000	-0.00933	0.02042	0.04024	0.10468	-0.42294	0.00704
		0.7855	0.5515	0.2401	0.0022	<.0001	0.8372
	854	854	853	854	854	854	854
agecat	-0.00933	1.00000	-0.00077	-0.03124	-0.08399	-0.07040	0.07724
	0.7855		0.9819	0.3533	0.0124	0.0363	0.0216
	854	885	884	885	885	885	885
sex	0.02042	-0.00077	1.00000	0.02322	-0.02865	-0.03209	0.07499
	0.5515	0.9819		0.4905	0.3949	0.3406	0.0258
	853	884	884	884	884	884	884
duracat	0.04024	-0.03124	0.02322	1.00000	-0.00668	-0.03072	-0.02251
	0.2401	0.3533	0.4905		0.8428	0.3614	0.5037
	854	885	884	885	885	885	885
diagnosis	0.10468	-0.08399	-0.02865	-0.00668	1.00000	-0.18499	0.08486
	0.0022	0.0124	0.3949	0.8428		<.0001	0.0116
	854	885	884	885	885	885	885
LOT	-0.42294	-0.07040	-0.03209	-0.03072	-0.18499	1.00000	0.02242
	<.0001	0.0363	0.3406	0.3614	<.0001		0.5054
	854	885	884	885	885	885	885
dxcat	0.00704	0.07724	0.07499	-0.02251	0.08486	0.02242	1.00000
	0.8372	0.0216	0.0258	0.5037	0.0116	0.5054	
	854	885	884	885	885	885	885

Figure B4: VIF and Tolerance for Logistic Regression Model of CSF Use and Covariates in the Post-Period

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Tolerance	Variance Inflation
Intercept	**1**	0.06982	0.05266	1.33	0.1853	.	0
FNrisk	**1**	0.02584	0.01635	1.58	0.1144	0.84792	1.17936
agecat	**1**	-0.01477	0.00831	-1.78	0.0757	0.96898	1.03201
sex	**1**	0.01740	0.01538	1.13	0.2583	0.99103	1.00905
duracat	**1**	0.01122	0.03364	0.33	0.7388	0.99152	1.00855
diagnosis	**1**	-0.01718	0.02496	-0.69	0.4915	0.93334	1.07142
LOT	**1**	-0.00274	0.01256	-0.22	0.8276	0.81494	1.22708
dxcat	**1**	0.01109	0.01764	0.63	0.5297	0.97736	1.02317

Figure B5: Spearman Correlation for Logistic Regression Model of Dose Reduction and Covariates

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	FNrisk	agecat	sex	duracat	diagnosis	LOT	dxcat
FNrisk	1.00000	-0.02208	0.02771	0.00614	0.32993	-0.51091	-0.06029
		0.2720	0.1679	0.7601	<.0001	<.0001	0.0027
	2477	2477	2477	2477	2477	2477	2477
agecat	-0.02208	1.00000	0.02879	-0.01811	-0.01448	-0.03297	0.08348

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	FNrisk	agecat	sex	duracat	diagnosis	LOT	dxcat
	0.2720		0.1468	0.3615	0.4656	0.0966	<.0001
	2477	2541	2541	2541	2541	2541	2541
sex	0.02771	0.02879	1.00000	0.03335	0.03572	-0.01848	0.11565
	0.1679	0.1468		0.0928	0.0718	0.3518	<.0001
	2477	2541	2541	2541	2541	2541	2541
duracat	0.00614	-0.01811	0.03335	1.00000	-0.04510	-0.09047	-0.02450
	0.7601	0.3615	0.0928		0.0230	<.0001	0.2170
	2477	2541	2541	2541	2541	2541	2541
diagnosis	0.32993	-0.01448	0.03572	-0.04510	1.00000	-0.40375	0.02346
	<.0001	0.4656	0.0718	0.0230		<.0001	0.2372
	2477	2541	2541	2541	2541	2541	2541
LOT	-0.51091	-0.03297	-0.01848	-0.09047	-0.40375	1.00000	0.05828
	<.0001	0.0966	0.3518	<.0001	<.0001		0.0033
	2477	2541	2541	2541	2541	2541	2541
dxcat	-0.06029	0.08348	0.11565	-0.02450	0.02346	0.05828	1.00000
	0.0027	<.0001	<.0001	0.2170	0.2372	0.0033	
	2477	2541	2541	2541	2541	2541	2541

Figure B6: VIF and Tolerance Logistic Regression Model of dose reduction and Covariates

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Tolerance	Variance Inflation
Intercept	**1**	0.45738	0.09172	4.99	<.0001	.	0
FNrisk	**1**	0.14869	0.04859	3.06	0.0023	0.79203	1.26259
agecat	**1**	-0.00497	0.02701	-0.18	0.8541	0.97415	1.02653
sex	**1**	0.03297	0.04444	0.74	0.4585	0.98536	1.01485
duracat	**1**	0.17137	0.03897	4.40	<.0001	0.98743	1.01273
diagnosis	**1**	0.00016828	0.03976	0.00	0.9966	0.79728	1.25426
LOT	**1**	-0.01289	0.03667	-0.35	0.7253	0.73699	1.35687
dxcat	**1**	0.09624	0.05247	1.83	0.0673	0.97451	1.02616

Figure B7: Spearman correlation for Logistic Regression Model of Mortality and Covariates

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	csfuse	dosered	FNrisk	agecat	sex	duracat	diagnosis	LOT	dxcat
csfuse	1.00000	-0.21831	0.08197	-0.07152	0.04875	0.05092	0.01328	-0.03515	-0.03303
	2497	<.0001	<.0001	0.0003	0.0148	0.0109	0.5072	0.0790	0.0989
		2497	2433	2497	2497	2497	2497	2497	2497

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	csfuse	dosered	FNrisk	agecat	sex	duracat	diagnosis	LOT	dxcat
dosered	-0.21831 <.0001 464	1.00000 464	0.16262 0.0004 464	-0.00785 0.8661 464	0.03843 0.4088 464	0.21017 <.0001 464	0.05972 0.1991 464	-0.07879 0.0900 464	0.06246 0.1792 464
FNrisk	0.08197 <.0001 2433	0.16262 0.0004 464	1.00000 2477	-0.02208 0.2720 2477	0.02771 0.1679 2477	0.00614 0.7601 2477	0.32993 <.0001 2477	-0.51091 <.0001 2477	-0.06029 0.0027 2477
agecat	-0.07152 0.0003 2497	-0.00785 0.8661 464	-0.02208 0.2720 2477	1.00000 2541	0.02879 0.1468 2541	-0.01811 0.3615 2541	-0.01448 0.4656 2541	-0.03297 0.0966 2541	0.08348 <.0001 2541
sex	0.04875 0.0148 2497	0.03843 0.4088 464	0.02771 0.1679 2477	0.02879 0.1468 2541	1.00000 2541	0.03335 0.0928 2541	0.03572 0.0718 2541	-0.01848 0.3518 2541	0.11565 <.0001 2541
duracat	0.05092 0.0109 2497	0.21017 <.0001 464	0.00614 0.7601 2477	-0.01811 0.3615 2541	0.03335 0.0928 2541	1.00000 2541	-0.04510 0.0230 2541	-0.09047 <.0001 2541	-0.02450 0.2170 2541
diagnosis	0.01328 0.5072 2497	0.05972 0.1991 464	0.32993 <.0001 2477	-0.01448 0.4656 2541	0.03572 0.0718 2541	-0.04510 0.0230 2541	1.00000 2541	-0.40375 <.0001 2541	0.02346 0.2372 2541

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	csfuse	dosered	FNrisk	agecat	sex	duracat	diagnosis	LOT	dxcat
				2541		2541		2541	
LOT	-0.03515	-0.07879	-0.51091	-0.03297	-0.01848	-0.09047	-0.40375	1.00000	0.05828
	0.0790	0.0900	<.0001	0.0966	0.3518	<.0001	<.0001	2541	0.0033 2541
	2497	464	2477	2541	2541	2541	2541		
dxcat	-0.03303	0.06246	-0.06029	0.08348	0.11565	-0.02450	0.02346	0.05828	1.00000
	0.0989	0.1792	0.0027	<.0001	<.0001	0.2170	0.2372	0.0033	
	2497	464	2477	2541	2541	2541	2541	2541	2541

Figure B8: VIF and Tolerance Logistic Regression Model of Mortality and Covariates

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Tolerance	Variance Inflation
Intercept	**1**	0.67920	0.08255	8.23	<.0001	.	0
csfuse	**1**	0.05428	0.12309	0.44	0.6595	0.91207	1.09641
dosered	**1**	-0.05686	0.04154	-1.37	0.1717	0.87832	1.13854
FNrisk	**1**	-0.12458	0.04269	-2.92	0.0037	0.76591	1.30563
agecat	**1**	0.06128	0.02335	2.62	0.0090	0.97268	1.02809
sex	**1**	-0.10985	0.03841	-2.86	0.0044	0.98413	1.01612
duracat	**1**	-0.12127	0.03438	-3.53	0.0005	0.94685	1.05613

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Tolerance	Variance Inflation
diagnosis	**1**	0.10154	0.03436	2.96	0.0033	0.79711	1.25453
LOT	**1**	0.07961	0.03169	2.51	0.0124	0.73640	1.35796
dxcat	**1**	-0.04112	0.04598	-0.89	0.3716	0.94703	1.05593

Figure B9: Spearman correlation for Logistic Regression Model of Mortality and Compare

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	compare	FNrisk	agecat	sex	duracat	diagnosis	LOT
compare	1.00000	0.00506	-0.48878	0.06098	-0.03359	0.02421	0.10791
		0.9029	<.0001	0.1364	0.4122	0.5546	0.0083
	598	584	598	598	598	598	598
FNrisk	0.00506	1.00000	-0.02208	0.02771	0.00614	0.32993	-0.51091
	0.9029		0.2720	0.1679	0.7601	<.0001	<.0001
	584	2477	2477	2477	2477	2477	2477
agecat	-0.48878	-0.02208	1.00000	0.02879	-0.01811	-0.01448	-0.03297
	<.0001	0.2720		0.1468	0.3615	0.4656	0.0966
	598	2477	2541	2541	2541	2541	2541
sex	0.06098	0.02771	0.02879	1.00000	0.03335	0.03572	-0.01848
	0.1364	0.1679	0.1468		0.0928	0.0718	0.3518
	598	2477	2541	2541	2541	2541	2541
duracat	-0.03359	0.00614	-0.01811	0.03335	1.00000	-0.04510	-0.09047
	0.4122	0.7601	0.3615	0.0928		0.0230	<.0001

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	compare	FNrisk	agecat	sex	duracat	diagnosis	LOT
	598	2477	2541	2541	2541	2541	2541
diagnosis	0.02421	0.32993	-0.01448	0.03572	-0.04510	1.00000	-0.40375
	0.5546	<.0001	0.4656	0.0718	0.0230		<.0001
	598	2477	2541	2541	2541	2541	2541
LOT	0.10791	-0.51091	-0.03297	-0.01848	-0.09047	-0.40375	1.00000
	0.0083	<.0001	0.0966	0.3518	<.0001	<.0001	
	598	2477	2541	2541	2541	2541	2541

Figure B10: VIF and Tolerance for Logistic Regression Model of Mortality and Compare

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Tolerance	Variance Inflation
Intercept	**1**	0.54642	0.07783	7.02	<.0001	.	0
compare	**1**	-0.04660	0.04226	-1.10	0.2706	0.76034	1.31520
FNrisk	**1**	-0.05016	0.04164	-1.20	0.2288	0.78758	1.26971
agecat	**1**	0.11512	0.02218	5.19	<.0001	0.76899	1.30041
sex	**1**	-0.16339	0.03746	-4.36	<.0001	0.97963	1.02079
duracat	**1**	-0.07973	0.03203	-2.49	0.0131	0.96380	1.03756
diagnosis	**1**	0.04209	0.03476	1.21	0.2264	0.82979	1.20512
LOT	**1**	0.11416	0.03473	3.29	0.0011	0.72544	1.37846

ACRONYMS

ABIM American Board of Internal Medicine

ACS American Cancer Society

AJCC American Joint Committee on Cancer

ANC Absolute Neutrophil Count

API Asian & Pacific Islanders

ASCO American Society of Clinical Oncology

CanCORS Cancer Care Outcomes Research and Surveillance

CBC Complete Blood Count

CT Computed Topography

CSF Colony Stimulating Factors

DCBE Double-Contrast Barium Enema

EGFR Epidermal Growth Factor Receptor

EORTC European Organization for Research and Treatment of Cancer

ESMO European Society of Medical Oncology

FIT Fecal Immunochemical Test

FN Febrile Neutropenia

G-CSF Granulocyte Colony Stimulating Factors

GM-CSF Granulocyte Macrophage Colony Stimulating Factors

gFOBT Guaiac-based Fecal Occult Blood Tests

iFOBT Immunochemical Fecal Occult Blood Test

IL-3 Interleukin 3

IRB Institutional Review Board

LOT Line of Therapy

MASCC Multinational Association of Supportive Care in Cancer

M-CSF Macrophage Colony Stimulating Factors

MEPS Medical Expenditure Panel Survey

NCCN National Comprehensive Cancer Network

NHB Non-Hispanic Blacks

NHW Non-Hispanic Whites

OCM Oncology Care Model

RCT Randomized Controlled Trials

RDI Reduced Dose Intensity

SEER Surveillance, Epidemiology and End Results

TNM Tumor, Lymph Nodes, Metastasis

USPSTF United States Preventive Services Task Force

VEGF Vascular Endothelial Growth Factor Inhibitor

VIF Variance Inflation Factor

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